Pembrolizumab (Keytruda®)

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

POLICY

I. INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

A. FDA-Approved Indications

1. Melanoma
   - i. Keytruda (pembrolizumab) is indicated for the treatment of patients with unresectable or metastatic melanoma.
   - ii. Keytruda is indicated for the adjuvant treatment of adult and pediatric (12 years and older) patients with Stage IIB, IIC, or III melanoma following complete resection.

2. Non-Small Cell Lung Cancer
   - i. Keytruda, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
   - ii. Keytruda, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of patients with metastatic squamous NSCLC.
   - iii. Keytruda, as a single agent, is indicated 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:
     - a. stage III where patients are not candidates for surgical resection or definitive chemoradiation, or
     - b. metastatic.
   - iv. Keytruda, as a single agent, is indicated 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.
   - v. Keytruda, in combination with platinum-containing chemotherapy, is indicated for the treatment of patients with resectable (tumors ≥4 cm or node positive) NSCLC as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.
   - vi. Keytruda, as a single agent, is indicated for adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage 1B (T2a ≥ 4cm), II, or IIIA NSCLC

3. Head and Neck Squamous Cell Cancer

i. Keytruda, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
ii. Keytruda, as a single agent, is indicated 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.
iii. Keytruda, as a single agent, is indicated for the treatment of patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

4. Classical Hodgkin Lymphoma
   i. Keytruda is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL).
   ii. Keytruda is indicated for the treatment of pediatric patients with refractory cHL, or cHL that has relapsed after 2 or more prior lines of therapy.

5. Primary Mediastinal Large B-cell Lymphoma
   Keytruda is indicated for the treatment of adult and pediatric patients with refractory primary mediastinal large B-cell lymphoma (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.

6. Urothelial Carcinoma
   i. Keytruda, as a single agent, is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma:
      a. who are not eligible for any platinum-containing chemotherapy, or
      b. who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
   ii. Keytruda, as a single agent, is indicated 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.
   iii. Keytruda, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial carcinoma.

7. Microsatellite Instability-High Cancer or Mismatch Repair Deficient Cancer
   Keytruda is indicated for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options.

8. Microsatellite Instability-High or Mismatch Repair Deficient Colorectal Cancer (CRC)
   Keytruda is indicated for the treatment of patients with unresectable or metastatic MSI-H or dMMR colorectal cancer (CRC) as determined by an FDA-approved test.

9. Gastric Cancer
   i. Keytruda, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ)

adenocarcinoma whose tumors express P-L1 (CPS≥1) as determined by an FDA-approved test.

ii. Keytruda, in combination with fluoropyrimidine- and platinum-containing chemotherapy is indicated for the first-line treatment of adults with locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma.

10. Esophageal Cancer
    Keytruda is indicated 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
    i. Keytruda in combination with chemotherapy, with or without bevacizumab, is indicated 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.
    ii. Keytruda, as a single agent, is indicated for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumor express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.
    iii. Keytruda, in combination with chemoradiotherapy (CRT), is indicated for the treatment of patients with FIGO 2014 Stage III-IVA cervical cancer.

12. Hepatocellular Carcinoma
    Keytruda is indicated for the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.

13. Biliary Tract Cancer
    Keytruda, in combination with gemcitabine and cisplatin is indicated for the treatment of patients with locally advanced unresectable or metastatic biliary tract cancer (BTC).

14. Merkel Cell Carcinoma
    Keytruda is indicated for the treatment of adult and pediatric patients with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

15. Renal Cell Carcinoma
    i. Keytruda, in combination with axitinib, is indicated for the first-line treatment of patients with advanced renal cell carcinoma (RCC).
    ii. Keytruda, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC
    iii. Keytruda is indicated 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

16. Endometrial Carcinoma
    i. Keytruda, in combination with lenvatinib, is indicated for the treatment of patients with advanced endometrial carcinoma that is mismatch repair proficient (pMMR) as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation.

ii. Keytruda, as a single agent, is indicated 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.

17. Tumor Mutational Burden-High Cancer
    Keytruda is indicated 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.

18. Cutaneous Squamous Cell Carcinoma
    Keytruda is indicated for the treatment of patients with recurrent or metastatic cutaneous squamous cell carcinoma (cSCC) or locally advanced cSCC that is not curable by surgery or radiation.

19. Triple-Negative Breast Cancer
    i. Keytruda, in combination with chemotherapy, is indicated for the treatment of patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.
    ii. Keytruda is indicated for the treatment of patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as a single agent as adjuvant treatment after surgery.

19. Adult Classical Hodgkin Lymphoma and Adult Primary Mediastinal Large B-Cell Lymphoma: Additional Dosing Regimen of 400mg Every 6 Weeks
    Keytruda is indicated for use at an additional recommended dosage of 400mg every 6 weeks for classical Hodgkin lymphoma and primary mediastinal large B-cell lymphoma in adults.

B. Compendial Uses
1. Cutaneous melanoma
2. Non-small cell lung cancer
3. Head and neck squamous cell cancer
4. Classical Hodgkin Lymphoma
5. Urothelial carcinoma
    i. Bladder cancer
    ii. Primary carcinoma of the urethra
    iii. Upper genitourinary tract tumors
    iv. Urothelial carcinoma of the prostate
6. Anaplastic thyroid carcinoma
7. Follicular, Oncocytic (hürthle cell), or papillary thyroid carcinoma
8. Medullary thyroid carcinoma
9. Colorectal cancer
10. Small bowel adenocarcinoma
11. Gastric cancer and esophagogastric junction cancer
12. Esophageal cancer
13. Cervical cancer
14. Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer

15. Uveal melanoma
16. Testicular cancer
17. Endometrial carcinoma
18. Anal carcinoma
19. Central Nervous System (CNS) brain metastases
20. Primary mediastinal large B-cell lymphoma
21. Pancreatic adenocarcinoma
22. Biliary Tract cancers
23. Vulvar cancer
24. Renal cell carcinoma
25. Thymic carcinoma
26. Primary Cutaneous Lymphomas
    i. Mycosis Fungoides/Sezary syndrome
    ii. Anaplastic Large Cell Lymphoma (ALCL)
27. Extranodal NK/T-cell lymphoma
28. Gestational trophoblastic neoplasia
29. Neuroendocrine and Adrenal Tumors
    i. Well Differentiated Grade 3 Tumors
    ii. Adrenal Gland Tumors
    iii. Extrapulmonary Poorly Differentiated/Large or Small Cell Tumors
    iv. Adrenocortical carcinoma
30. Soft tissue sarcomas
    i. alveolar soft part sarcoma (ASPS)
    ii. cutaneous angiosarcoma
    iii. extremity/body wall sarcoma
    iv. head/neck sarcoma
    v. retroperitoneal/intra-abdominal sarcoma
    vi. rhabdomyosarcoma
31. Occult primary cancer
32. Prostate cancer
33. Bone Cancer
    i. Chondrosarcoma
    ii. Chordoma
    iii. Ewing Sarcoma
    iv. Osteosarcoma
34. Breast Cancer
35. Salivary Gland Tumors
36. Merkel Cell Carcinoma
37. Penile Cancer
38. Uterine Sarcoma
39. Small cell lung cancer
40. Ampullary Adenocarcinoma
41. Pediatric Diffuse High-Grade Gliomas
42. Cutaneous squamous cell carcinoma
43. Nasopharyngeal Cancer
44. Kaposi Sarcoma

All other indications are considered experimental/investigational and not medically necessary.

II. DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

A. Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
B. Documentation of laboratory report confirming microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumor status, where applicable.
C. Documentation of laboratory report confirming high tumor mutational burden (≥10 mutations/megabase [mut/Mb]), where applicable.
D. Documentation of laboratory report confirming that the cancer cells are negative for the following receptors, where applicable:
    1. human epidermal growth factor receptor 2 (HER-2)
    2. estrogen
    3. progesterone
E. Documentation of the presence of EGFR exon 19 deletions or L858R mutations or ALK rearrangements, where applicable.

III. EXCLUSIONS

Coverage will not be provided for members with any of the following exclusions:

A. Pediatric members with TMB-H central nervous system cancers.
B. Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy (other than when used as second-line or subsequent therapy for metastatic or unresectable melanoma in combination with ipilimumab following progression on single agent anti-PD-1 immunotherapy).

IV. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

Authorization of 6 months may be granted for treatment of cutaneous melanoma in any of the following settings:

1. For unresectable, recurrent, or metastatic disease as a single agent.
2. As subsequent therapy for disease progression of metastatic or unresectable tumors, as a single agent or in combination with ipilimumab or lenvatinib.
3. As adjuvant treatment following complete lymph node resection or complete resection of stage IIB, IIC, III, or metastatic disease as a single agent.
4. As subsequent or re-induction therapy in combination with trametinib and dabrafenib for metastatic or unresectable disease with a BRAF V600 activating mutation.

B. Non-small Cell Lung Cancer (NSCLC)

1. Authorization of 6 months may be granted for treatment of recurrent, advanced, or metastatic NSCLC when there are no EGFR exon 19 deletions or L858R mutations or ALK rearrangements (unless testing is not feasible due to insufficient tissue) and any of the following criteria are met:
    i. The requested medication will be used as a first-line therapy for PDL1 positive disease.
    ii. The requested medication will be used as single agent or in combination with pemetrexed for maintenance therapy.
    iii. The requested medication will be used in combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology.
    iv. The requested medication will be used in combination with carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology.
2. Authorization of 6 months may be granted as neoadjuvant treatment when used in combination with platinum containing chemotherapy for resectable (tumors ≥4 cm or node positive) NSCLC, and then continued as single agent adjuvant therapy after surgery.

3. Authorization of 6 months may be granted as a single agent for adjuvant treatment following resection and platinum-based chemotherapy for stage IB (T2a ≥4 cm), II, or III NSCLC.
4. Authorization of 6 months may be granted for single agent subsequent treatment of PDL1 positive recurrent, advanced, or metastatic NSCLC.

C. Head and Neck Squamous Cell Cancer

Authorization of 6 months may be granted for treatment of members with very advanced head and neck squamous cell carcinoma with mixed subtypes (HNSCC) and nasopharyngeal cancer when any of the following criteria is met:

1. The requested medication will be used as a single agent for first-line treatment in members whose tumors express PD-L1 (CPS ≥1), are microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden high (TMB-H [≥ 10 mut/Mb].
2. The requested medication will be used as a single agent for subsequent therapy.
3. The requested medication will be used in combination with cetuximab or chemotherapy.

D. Classical Hodgkin Lymphoma

Authorization of 6 months may be granted as a single agent or in combination with GVD (gemcitabine, vinorelbine, liposomal doxorubicin) or ICE (ifosfamide, carboplatin, etoposide) for treatment of relapsed, refractory or progressive classical Hodgkin lymphoma.

E. Urothelial Carcinoma

1. Authorization of 6 months may be granted as a single agent for treatment of urothelial carcinoma when used in any of the following subtypes:
   i. Urothelial carcinoma of the bladder in any of the following settings:
      a. First line therapy for locally advanced or metastatic disease in members who are not eligible for any platinum containing chemotherapy.
      b. Subsequent therapy.
      c. For the treatment of members with high risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) when disease is Bacillus Calmette Guerin (BCG) unresponsive, and member will not undergo cystectomy.
   ii. Primary carcinoma of the urethra with locally advanced, recurrent or metastatic disease post-platinum or other chemotherapy or for members who are not eligible for any platinum-containing chemotherapy.
   iii. Urothelial carcinoma of the upper genitourinary tract or urothelial carcinoma of the prostate with metastatic disease post-platinum or other chemotherapy or for members who are not eligible for any platinum-containing chemotherapy.
2. Authorization of 6 months may be granted for the treatment of stage II, recurrent, locally advanced or metastatic urothelial carcinoma in combination with enfortumab vedotin-ejfv.

F. Solid Tumors

Authorization of 6 months may be granted as a single agent for treatment of solid tumors in members with unresectable or metastatic disease that has progressed following prior treatment and who have no satisfactory alternative treatment options when either of the following criteria is met:

1. The requested medication will be used for microsatellite instability-high or mismatch repair deficient solid tumors.
2. The requested medication will be used for tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) solid tumors.

G. Anaplastic Thyroid Carcinoma

1. Authorization of 6 months may be granted as a single agent for treatment of metastatic anaplastic thyroid carcinoma for tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors.

2. Authorization of 6 months may be granted in combination with lenvatinib (Lenvima) for treatment of stage IVC anaplastic thyroid carcinoma.

H. Follicular, Oncocytic (Hürthle Cell), or Papillary Thyroid Carcinoma
Authorization of 6 months may be granted for treatment of unresectable or metastatic follicular, oncocytic (hürthle cell), or papillary thyroid carcinoma for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors not amenable to radioactive iodine therapy.

I. Medullary Thyroid Carcinoma
Authorization of 6 months may be granted for treatment of unresectable, recurrent, or metastatic medullary thyroid carcinoma for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden-high (≥10 mutations/megabase [mut/Mb]) tumors.

J. Colorectal Cancer
Authorization of 6 months may be granted as a single agent for the treatment of inoperable, advanced, or metastatic colorectal cancer, including appendiceal carcinoma, for microsatellite instability-high or mismatch repair deficient tumors.

K. Small Bowel Adenocarcinoma
Authorization of 6 months may be granted as a single agent for treatment of advanced or metastatic small bowel adenocarcinoma for microsatellite instability-high or mismatch repair deficient tumors.

L. Merkel Cell Carcinoma
Authorization of 6 months may be granted as a single agent for treatment of Merkel cell carcinoma in members with recurrent or metastatic disease.

M. Gastric Cancer
1. Authorization of 6 months may be granted for treatment of gastric cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when any of the following criteria are met:
   i. The requested medication will be used as subsequent therapy as a single agent for microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) or tumor mutational burden (TMB) high (≥10 mutations/megabase (mut/Mb)).
   ii. The requested medication will be used as first line therapy as a single agent or in combination with chemotherapy for microsatellite instability-high or deficient mismatch repair tumors.
   iii. The requested medication will be used in combination with trastuzumab, and chemotherapy for HER2 overexpression positive adenocarcinoma.
   iv. The requested medication will be used in combination with chemotherapy for the first-line treatment of HER2-negative adenocarcinoma.
2. Authorization of 6 months may be granted for treatment of gastric cancer in members who are surgical candidates when any of the following criteria are met:
   i. The requested medication will be used as a single agent or in combination with chemotherapy to treat microsatellite instability-high or deficient mismatch repair tumors.
   ii. The requested medication will be used in combination with trastuzumab and chemotherapy to treat surgically unresectable locoregional disease that is HER2 positive.

N. Esophageal Cancer and Esophagogastric Junction (EGJ) Cancer
1. Authorization of 6 months may be granted as a single agent for treatment of esophageal and EGJ cancer in members who are surgical candidates when the requested medication will be used to treat microsatellite instability-high or deficient mismatch repair tumors.

2. Authorization of 6 months may be granted for treatment of esophageal cancer (including EGJ cancer) in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when any of the following conditions are met:
   i. The requested medication will be used as subsequent therapy as a single agent for microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR), or tumor mutational burden (TMB) high (≥10 mutations/megabase (mut/Mb)) tumors.
   ii. The requested medication will be used as first line therapy as a single agent or in combination with platinum and fluoropyrimidine- based chemotherapy for microsatellite instability-high or deficient mismatch repair tumors.
   iii. The requested medication will be used as single agent subsequent therapy with PD-L1 tumor expression by CPS ≥ 10 for squamous cell carcinoma.
   iv. The requested medication will be used in combination with platinum and fluoropyrimidine-based chemotherapy for squamous cell carcinoma or HER2 overexpression negative adenocarcinoma.
   v. The requested medication will be used in combination with trastuzumab, platinum and fluoropyrimidine-based chemotherapy for HER2 overexpression positive adenocarcinoma.

O. Cervical Cancer

Authorization of 6 months may be granted for the treatment of cervical cancer when any of the following criteria are met:

1. Persistent, recurrent or metastatic disease in combination with chemotherapy with or without bevacizumab in members whose tumors express PD-L1 (CPS ≥1).
2. Recurrent or metastatic disease as single agent subsequent therapy in members whose tumors express PD-L1 (CPS ≥1) or are microsatellite instability-high or mismatch repair deficient.
3. Recurrent or metastatic disease and the member has experienced disease progression on or after chemotherapy for tumors that express PD-L1 (CPS ≥ 1), as a single agent.
4. FIGO stage III-IVA disease in combination with chemoradiotherapy (CRT).

P. Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer

Authorization of 6 months may be granted as a single agent for treatment of epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), clear cell carcinoma of the ovary, mucinous carcinoma of the ovary, grade 1 endometrioid carcinoma, low-grade serous carcinoma for recurrent or persistent microsatellite instability-high or mismatch repair deficient tumors or tumor mutational burden-high (TMB-H) (tumors ≥10 mutations/megabase [mut/Mb]).

Q. Uveal Melanoma

Authorization of 6 months may be granted as a single agent for treatment of unresectable or metastatic uveal melanoma.

R. Testicular Cancer

Authorization of 6 months may be granted as a single agent for third-line therapy for treatment of testicular cancer in members with microsatellite instability-high or mismatch repair deficient or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase [mut/Mb]) tumors.

S. Endometrial Carcinoma

1. Authorization of 6 months may be granted in combination with lenvatinib for treatment of advanced, metastatic, or recurrent endometrial carcinoma when either of the following criteria are met:
   i. The disease is mismatch repair proficient (pMMR)
   ii. The disease is mismatch repair deficient (dMMR) and has progressed following prior platinum-based chemotherapy

2. Authorization of 6 months may be granted as a single agent for treatment of endometrial carcinoma in members with recurrent unresectable or metastatic microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden high (TMB-H) [≥ 10 mut/Mb] tumors
3. Authorization of 6 months may be granted for treatment of endometrial carcinoma in combination with carboplatin and paclitaxel in members with stage III-IV or recurrent disease

T. Anal Carcinoma

Authorization of 6 months may be granted as a single agent for subsequent treatment of metastatic anal carcinoma.

U. CNS Brain Metastases

Authorization of 6 months may be granted as a single agent for treatment of CNS brain metastases in members with melanoma or PD-L1 positive non-small cell lung cancer.

V. Primary Mediastinal Large B-Cell Lymphoma

Authorization of 6 months may be granted as a single agent or in combination with brentuximab vedotin for treatment of primary mediastinal large B-cell lymphoma in members with relapsed or refractory disease.

W. Pancreatic Adenocarcinoma

Authorization of 6 months may be granted as a single agent for treatment of recurrent, locally advanced or metastatic pancreatic adenocarcinoma in members with microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden high (TMB-H) [≥ 10 mut/Mb] tumors.

X. Biliary Tract Cancers

1. Authorization of 6 months may be granted in combination with gemcitabine and cisplatin for locally advanced unresectable, resected gross residual (R2) disease or metastatic biliary tract cancers.
2. Authorization of 6 months may be granted as a single agent for unresectable, resected gross residual (R2) disease, or metastatic biliary cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer that is microsatellite instability-high, mismatch repair deficient or tumor mutational burden high (TMB-H) [≥ 10 mut/Mb].

Y. Hepatocellular Carcinoma

Authorization of 6 months may be granted for treatment of hepatocellular carcinoma when any of the following criteria are met:

1. The member has previously been treated with sorafenib
2. The member has unresectable, inoperable or metastatic disease, or disease with extensive liver tumor burden and will use the requested medication as single agent subsequent treatment.

Z. Vulvar Cancer

Authorization of 6 months may be granted as a single agent for subsequent treatment of advanced, recurrent, or metastatic disease in members with vulvar cancer when either of the following criteria is met:

1. Member has microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or tumor mutational burden high (TMB-H [≥ 10 mut/Mb] tumors.
2. Member has experienced disease progression on or after chemotherapy and whose tumor expresses PD-L1 (CPS ≥ 1).

AA. Renal Cell Carcinoma

Authorization of 6 months may be granted for treatment of renal cell carcinoma, when any of the following criteria are met:

1. The requested medication will be used as first-line treatment in combination with axitinib or lenvatinib for advanced, relapsed or stage IV disease.
2. The requested medication will be used as subsequent therapy in combination with axitinib or lenvatinib for relapsed or stage IV disease with clear cell histology.
3. The requested medication will be used as a single agent for relapsed or stage IV disease with non-clear cell histology.
4. The requested medication will be used as a single agent for the adjuvant treatment of members with RCC at intermediate-high or high risk of recurrence following nephrectomy or following nephrectomy and resection of metastatic lesions.

BB. Thymic Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of thymic carcinoma for unresectable, locally advanced, or metastatic disease, or as pre or postoperative therapy for residual tumor in members who cannot tolerate first-line combination regimens.

CC. Primary Cutaneous Lymphomas

Authorization of 6 months may be granted for treatment of primary cutaneous lymphomas when either of the following is met:

1. Member has a diagnosis of mycosis fungoides/Sezary syndrome.
2. Member has a diagnosis of relapsed or refractory anaplastic large cell lymphoma (ALCL) and the requested medication will be used as a single agent.

DD. Extranodal NK/T-cell lymphoma

Authorization of 6 months may be granted for treatment of extranodal NK/T-cell lymphoma, in members with relapsed or refractory disease.

EE. Gestational Trophoblastic Neoplasia

Authorization of 6 months may be granted as a single agent for treatment of gestational trophoblastic neoplasia for multi-agent chemotherapy-resistant disease when either of the following criteria is met:

1. Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor)
2. Member has high-risk disease.

FF. Neuroendocrine and Adrenal Tumors

Authorization of 6 months may be granted for treatment of unresectable, locally advanced or metastatic neuroendocrine and adrenal tumors.

GG. Cutaneous Squamous Cell Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of locally advanced, recurrent or metastatic cutaneous squamous cell carcinoma that is not curable by surgery or radiation.

HH. Soft Tissue Sarcoma

Authorization of 6 months may be granted for treatment of the following types of soft tissue sarcoma when either of the following criteria are met:

1. The requested medication will be used as a single agent or in combination with axitinib (Inlyta) for the treatment of alveolar soft part sarcoma (ASPS).
2. The requested medication will be used as a single agent for the treatment of cutaneous angiosarcoma.
3. The requested medication will be used as a single agent for the subsequent treatment of extremity/body wall sarcoma, head/neck sarcoma, retroperitoneal/intra-abdominal sarcoma, and rhabdomyosarcoma.

II. Occult Primary Cancer

Authorization of 6 months may be granted as a single agent for treatment of occult primary cancer in members with microsatellite instability-high or mismatch repair deficient tumors or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase (mut/Mb) tumors).

JJ. Breast Cancer

1. Authorization of 6 months may be granted for treatment of patients with no response to preoperative systemic therapy or for recurrent unresectable or metastatic triple-negative breast cancer (TNBC) when all of the following criteria are met:
   - i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
     - a. Human epidermal growth factor receptor 2 (HER-2)
     - b. Estrogen
     - c. Progesterone
   - ii. Tumor must express PD-L1.
   - iii. The requested medication will be used as a single agent or in combination with chemotherapy.
2. Authorization of 6 months may be granted for treatment of high-risk early-stage triple-negative breast cancer (TNBC) when all of the following criteria are met:
   - i. The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
     - a. Human epidermal growth factor receptor 2 (HER-2)
     - b. Estrogen
     - c. Progesterone
   - ii. The requested medication will be used as either:
     - a. Neoadjuvant treatment in combination with chemotherapy; or
     - b. Continued adjuvant treatment after surgery, as a single agent.

KK. Prostate Cancer

Authorization of 6 months may be granted as single agent subsequent therapy for treatment of castration-resistant distant metastatic prostate cancer in members with microsatellite instability-high, mismatch repair deficient, or tumor mutational burden (TMB) ≥10 mutations/megabase tumors.

LL. Small Cell Lung Cancer

Authorization of 6 months may be granted as a single agent for subsequent therapy of relapsed or progressive disease.

MM. Pediatric Diffuse High-Grade Gliomas

Authorization of 6 months may be granted as adjuvant treatment for hypermutant tumor pediatric diffuse high-grade glioma or for recurrent or progressive disease.

NN. Ampullary Adenocarcinoma

Authorization of 6 months may be granted as a single agent for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb) ampullary adenocarcinoma.

OO. Kaposi Sarcoma

Authorization of 6 months may be granted as a single agent for subsequent treatment of relapsed/refractory endemic or classic Kaposi Sarcoma.

V. CONTINUATION OF THERAPY

A. Adjuvant treatment of melanoma, adjuvant high-risk early-stage TNBC, RCC, or NSCLC
Authorization of 6 months may be granted (up to 12 months total) for continued treatment in members requesting reauthorization for adjuvant treatment of cutaneous melanoma, high-risk early-stage TNBC, RCC or NSCLC who have not experienced disease recurrence or an unacceptable toxicity.

B. NSCLC, HNSCC, cHL, PMBCL, MSI-H or dMMR Cancers, Gastric Cancer, Esophageal Cancer, Cervical Cancer, HCC, MCC, RCC, Endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, TMB-H Cancer, Biliary Tract Cancer
Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for NSCLC, HNSCC, cHL, PMBCL, MSI-H or dMMR cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, locally recurrent unresectable or metastatic TNBC, TMB-H, and biliary tract cancers who have not experienced disease progression or unacceptable toxicity.

C. Urothelial Carcinoma
1. Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for urothelial carcinoma when the requested medication is used in combination with enfortumab vedotin-ejfv who have not experienced disease progression or an unacceptable toxicity.
2. Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for urothelial carcinoma when both of the following criteria are met:
   a. Member has not experienced disease progression or unacceptable toxicity.
   b. For high-risk BCG-unresponsive non-muscle invasive bladder cancer only: disease is not persistent or recurrent.

D. All other indications
Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication listed in Section IV who have not experienced disease progression or an unacceptable toxicity.

MEDICATION QUANTITY LIMITS

Drug Name	Diagnosis	Maximum Dosing Regimen
Keytruda (Pembrolizumab)	Ampullary Adenocarcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Anal Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks 2mg/kg every 3 weeks
Keytruda (Pembrolizumab)	Biliary Tract Cancer: Gallbladder Cancer, Intrahepatic/ Extrahepatic Cholangiocarcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Bone Cancer (Chondrosarcoma, Ewing Sarcoma, Osteosarcoma, or Chordoma)	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Breast Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks

Keytruda (Pembrolizumab)	Central Nervous System (CNS) Cancer - Brain Metastases	Route of Administration: Intravenous 10mg/kg every 2 weeks 200mg every 2 weeks
Keytruda (Pembrolizumab)	Cervical Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Classical Hodgkin Lymphoma	Route of Administration: Intravenous ≥18 Years 200mg every 3 weeks 400mg every 6 weeks ≤17 Years 2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Colorectal Cancer or Appendiceal Adenocarcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks 2mg/kg every 3 weeks
Keytruda (Pembrolizumab)	Cutaneous Squamous Cell Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Endometrial Carcinoma, Uterine Sarcoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Esophageal Cancer, Gastric Cancer or Gastroesophageal Junction Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Extranodal NK/T-Cell Lymphomas, Primary Cutaneous Lymphoma, including Mycosis Fungoides/ Sezary Syndrome or Anaplastic Large Cell Lymphoma (ALCL)	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Fallopian Tube Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Gestational Trophoblastic Neoplasia	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Head and Neck Squamous Cell Carcinoma or Nasopharyngeal Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Hepatocellular Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Kaposi Sarcoma	Route of Administration: Intravenous 200mg every 3 weeks
Keytruda (Pembrolizumab)	Melanoma or Melanoma, Uveal	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Melanoma, Adjuvant	Route of Administration: Intravenous 12-17 Years

		2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Merkel Cell Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks ≤17 Years 2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Microsatellite Instability-High or Mismatch Repair Deficient Cancer	Route of Administration: Intravenous ≥18 Years 200mg every 3 weeks 400mg every 6 weeks ≤17 Years 2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Neuroendocrine Tumor or Adrenal Gland Tumor (Adrenocortical Carcinoma)	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Non-Small Cell Lung Cancer or Small Cell Lung Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Occult Primary Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Ovarian Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Pancreatic Adenocarcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Pediatric Diffuse High-Grade Gliomas	Route of Administration: Intravenous < 18 Years 200mg every 3 weeks
Keytruda (Pembrolizumab)	Penile Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Primary Mediastinal Large B-cell Lymphoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks ≤17 Years 2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Primary Peritoneal Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Prostate Cancer	Route of Administration: Intravenous 200mg every 3 weeks

		400mg every 6 weeks
Keytruda (Pembrolizumab)	Renal Cell Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Salivary Gland Tumors	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Small Bowel Adenocarcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks 2mg/kg every 3 weeks
Keytruda (Pembrolizumab)	Soft Tissue Sarcoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Testicular Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Thymic Carcinoma	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Thyroid Carcinoma (Anaplastic, Follicular, Hurthle Cell, Medullary, or Papillary)	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Tumor Mutational Burden-High Cancer	Route of Administration: Intravenous ≥18 Years 200mg every 3 weeks 400mg every 6 weeks ≤17 Years 2mg/kg every 3 weeks (up to a maximum of 200 mg)
Keytruda (Pembrolizumab)	Urothelial Carcinoma (Bladder Cancer, Primary Carcinoma of the Urethra, Upper Genitourinary Tract Tumor, or Urothelial Carcinoma of the Prostate)	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks
Keytruda (Pembrolizumab)	Vulvar Cancer	Route of Administration: Intravenous 200mg every 3 weeks 400mg every 6 weeks

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice

Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

REFERENCES

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EFFECTIVE DATE 10/31/2024

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