Pembrolizumab and Berahyaluronidase alfa-pmph (Keytruda Qlex™)

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.

The proposal is to add text/statements in red and to delete text/statements with strikethrough:
POLICY

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.

FDA-Approved Indication(s)

Melanoma

- Keytruda Qlex is indicated for the treatment of adult patients with unresectable or metastatic melanoma.
- Keytruda Qlex is indicated for the adjuvant treatment of adult and pediatric patients 12 years and older with Stage IIB, IIC, or III melanoma following complete resection.

Non-Small Cell Lung Cancer

- Keytruda Qlex, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with metastatic nonsquamous non-small cell lung cancer (NSCLC), with no EGFR or ALK genomic tumor aberrations.
- Keytruda Qlex, in combination with carboplatin and either paclitaxel or paclitaxel protein-bound, is indicated for the first-line treatment of adult patients with metastatic squamous NSCLC.
- Keytruda Qlex, as a single agent, is indicated for the first-line treatment of adult 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.
- Keytruda Qlex, as a single agent, is indicated for the treatment of adult 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 Qlex.
- Keytruda Qlex, is indicated for the treatment of adult 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.
- Keytruda Qlex, as a single agent, is indicated as adjuvant treatment following resection and platinum-based chemotherapy for adult patients with stage IB (T2a ≥ 4cm), II, or IIIA NSCLC.

Malignant Pleural Mesothelioma

Keytruda Qlex, in combination with pemetrexed and platinum chemotherapy, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic malignant pleural mesothelioma (MPM).

Head and Neck Squamous Cell Cancer

- Keytruda Qlex is indicated for the treatment of adult patients with resectable locally advanced HNSCC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥1] as determined by an FDA approved test, as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.
- Keytruda Qlex, in combination with platinum and fluorouracil (FU), is indicated for the first-line treatment of adult patients with metastatic or with unresectable, recurrent head and neck squamous cell carcinoma (HNSCC).
- Keytruda Qlex, as a single agent, is indicated for the first line treatment of adult 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.
- Keytruda Qlex, as a single agent, is indicated for the treatment of adult patients with recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy.

Urothelial Cancer

- Keytruda Qlex, in combination with enfortumab vedotin, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer.
- Keytruda Qlex, as a single agent, is indicated for the treatment of adult 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.
- Keytruda Qlex, in combination with enfortumab vedotin, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.
- Keytruda Qlex, 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.

Microsatellite Instability-High Cancer or Mismatch Repair Deficient Cancer
Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older 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.

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

Gastric Cancer

- Keytruda Qlex, 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 PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- Keytruda Qlex, 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 whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.

Esophageal Cancer
Keytruda Qlex is indicated for the treatment of adult 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:

- In combination with platinum- and fluoropyrimidine-based chemotherapy for patients with tumors that express PD-L1 (CPS ≥ 1) , 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

- Keytruda Qlex, in combination with chemoradiotherapy (CRT), is indicated for the treatment of adult patients with locally advanced cervical cancer involving the lower third of the vagina, with or without extension to pelvic sidewall, or hydronephrosis/non-functioning kidney, or spread to adjacent pelvic organs (FIGO 2014 Stage III-IVA).
- Keytruda Qlex, in combination with chemotherapy, with or without bevacizumab, is indicated for the treatment of adult patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test.
- Keytruda Qlex, as a single agent, is indicated for the treatment of adult 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
Keytruda Qlex is indicated for the treatment of adult patients with hepatocellular carcinoma (HCC) secondary to hepatitis B who have received prior systemic therapy other than a PD-1/PD-L1- containing regimen.

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

Merkel Cell Carcinoma
Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older with recurrent locally advanced or metastatic Merkel cell carcinoma (MCC).

Renal Cell Carcinoma

- Keytruda Qlex, in combination with axitinib, is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).
- Keytruda Qlex, in combination with lenvatinib, is indicated for the first-line treatment of adult patients with advanced RCC.
- Keytruda Qlex is indicated for the adjuvant treatment of adult patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions.

Endometrial Carcinoma

- Keytruda Qlex, in combination with carboplatin and paclitaxel, followed by Keytruda Qlex as a single agent, for the treatment of adult patients with primary advanced or recurrent endometrial carcinoma.
- Keytruda Qlex, in combination with lenvatinib, is indicated for the treatment of adult 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.
- Keytruda Qlex, as a single agent, is indicated for the treatment of adult 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 Cancer
Keytruda Qlex is indicated for the treatment of adult and pediatric patients 12 years and older 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 Qlex in pediatric patients 12 years and older with TMB-H central nervous system cancers have not been established.

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

Triple-Negative Breast Cancer
- Keytruda Qlex is indicated for the treatment of adult 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.
- Keytruda Qlex, in combination with chemotherapy, is indicated for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test.

Ovarian Cancer
Keytruda Qlex, in combination with paclitaxel, with or without bevacizumab, is indicated for the treatment of adult patients with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-authorized test, and who have received one or two prior systemic treatment regimens.

Compendial Uses

- Cutaneous melanoma
- Non-small cell lung cancer
- Head and neck cancer
- Urothelial carcinoma
  - Bladder cancer
  - Primary carcinoma of the urethra
  - Upper genitourinary tract tumors
  - Urothelial carcinoma of the prostate
- Appendiceal neoplasms and carcinoma
- Small bowel adenocarcinoma
- Merkel cell carcinoma
- Gastric cancer
- Esophageal cancer and esophagogastric junction cancer
- Cervical cancer

- Epithelial ovarian cancer/fallopian tube cancer/primary peritoneal cancer
- Uveal melanoma
- Endometrial carcinoma
- Anal carcinoma
- Central Nervous System (CNS) brain metastases
- Biliary tract cancers
- Hepatocellular carcinoma (HCC)
- Vulvar cancer
- Thymic carcinoma
- Gestational trophoblastic neoplasia
- Soft tissue sarcomas
  - Alveolar soft part sarcoma (ASPS)
  - Cutaneous angiosarcoma
  - Extremity/body wall sarcoma
  - Head/neck sarcoma
  - Retroperitoneal/intra-abdominal sarcoma
  - Rhabdomyosarcoma
  - Dedifferentiated liposarcoma
  - Epithelioid hemangioendothelioma
- Occult primary cancer
- Breast cancer
- Prostate cancer
- Bone Cancer
  - Chondrosarcoma
  - Chordoma
  - Ewing Sarcoma
  - Osteosarcoma
- Pediatric diffuse high-grade gliomas
- Vaginal cancer
- Pleural or peritoneal mesothelioma
- Penile cancer

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

DOCUMENTATION

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

- Documentation of programmed death ligand 1 (PD-L1) tumor expression, where applicable.
- Documentation of laboratory report confirming microsatellite instability-high (MSI-H), ~~or~~ mismatch repair (MMR) tumor status, or polymerase epsilon/delta (POLE/POLD1) tumor status with tumor mutational burden, where applicable.
- Documentation of laboratory report confirming high tumor mutational burden (≥10 mutations/megabase [mut/Mb]), where applicable.
- Documentation of laboratory report confirming that the cancer cells are negative for the following receptors, where applicable:
  - human epidermal growth factor receptor 2 (HER-2)
  - estrogen
  - progesterone

- Documentation of EGFR exon 19 deletions, exon 21 L858R mutations and ~~or~~ ALK, RET and ROS1 gene fusions, ~~tumor aberration status~~, where applicable.

EXCLUSIONS

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

- Pediatric members with TMB-H central nervous system cancers
- Members who have experienced disease progression while on programmed death receptor-1 (PD-1) or PD-L1 inhibitor therapy

COVERAGE CRITERIA

Cutaneous Melanoma

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

- For unresectable or metastatic disease as a single agent.
- As subsequent therapy for metastatic or unresectable disease, in combination with lenvatinib.
- As neoadjuvant treatment as a single agent.
- As adjuvant treatment following complete lymph node resection or complete resection of stage IIB, IIC, or III disease as a single agent in members 12 years of age or older.
- As subsequent or re-induction therapy in combination with trametinib and dabrafenib for metastatic or unresectable disease with a BRAF V600 activating mutation.

Non-Small Cell Lung Cancer (NSCLC)

Authorization of 6 months may be granted:

- For treatment of recurrent, advanced, or metastatic NSCLC when there are no EGFR exon 19 deletions or exon 21 L858R mutations, or ALK, RET or ROS1 gene fusions (unless testing is not feasible due to insufficient tissue) and any of the following criteria are met:
  - The requested medication will be used as a single agent for PDL1 positive disease.
  - The requested medication will be used as single agent or in combination with pemetrexed for maintenance therapy.
  - The requested medication will be used in combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology.
  - The requested medication will be used in combination with carboplatin and either paclitaxel or albumin-bound paclitaxel for squamous cell histology.
  - ~~In combination with pemetrexed and platinum chemotherapy for first-line treatment of metastatic nonsquamous NSCLC when there are no EGFR or ALK genomic tumor aberrations (unless testing is not feasible due to insufficient tissue)~~
  - ~~In combination with carboplatin and either paclitaxel or paclitaxel protein-bound for first-line treatment of metastatic squamous NSCLC~~
  - ~~For NSCLC whose tumors express PD-L1 (TPS ≥ 1 %) as a single agent and any of the following:~~
  - ~~First-line treatment of metastatic or Stage III disease where patients are not candidates for surgical resection or definitive chemoradiation~~
  - ~~Metastatic disease that has progressed on or after platinum-containing chemotherapy and FDA-approved targeted therapy, if tumor has EGFR or ALK genomic aberrations~~
- As neoadjuvant treatment when used in combination with platinum containing chemotherapy for resectable (tumors ≥4 cm or node positive) NSCLC, NSCLC when there are no EGFR exon 19 deletions or exon 21 L858R mutations, or ALK, RET, or ROS1 gene fusions (unless testing is not feasible due to insufficient tissue). ~~and then continued as single agent adjuvant therapy after surgery~~

- As adjuvant therapy ~~treatment~~ as a single agent after adjuvant chemotherapy or after neoadjuvant therapy with the requested medication plus chemotherapy when there are no EGFR exon 19 deletions or exon 21 L858R mutations, or ALK, RET or ROS1 gene fusions (unless testing is not feasible due to insufficient tissue). ~~following resection and platinum-based chemotherapy for Stage IB (T2a ≥4 cm), II, or IIIA NSCLC~~

Head and Neck Cancer

Authorization of 6 months may be granted for resectable stage III-IVa non-nasopharyngeal head and neck squamous cell carcinoma when PD-L1 ≥ 1 and the requested medication will be used as a single agent as neoadjuvant treatment, continued as adjuvant treatment in combination with radiotherapy (RT) with or without cisplatin and then as a single agent.

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

- 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].
- The requested medication will be used as a single agent for subsequent therapy.
- The requested medication will be used in combination with cetuximab or chemotherapy.

Authorization of 6 months may be granted for treatment of MSI-H, dMMR, TMB-H (≥ 10 mut/Mb), or PD-L1 positive recurrent salivary gland tumors as a single agent.

~~Authorization of 6 months may be granted for treatment of head and neck squamous cell carcinoma (HNSCC) in any of the following regimens:~~

- ~~In combination with platinum and fluorouracil for first-line treatment of metastatic or unresectable, recurrent disease~~
- ~~As a single agent for any of the following:~~
  - ~~First-line treatment of metastatic or unresectable, recurrent tumors expressing PD-L1 (CPS ≥ 1)~~
  - ~~Recurrent or metastatic disease with progression on or after platinum-containing chemotherapy~~

Urothelial Carcinoma ~~Cancer~~

Authorization of 6 months may be granted as a single agent for treatment of urothelial carcinoma ~~cancer~~ when used in any ~~that is either~~ of the following subtypes:

- Urothelial carcinoma of the bladder in any of the following settings:
  - First line therapy for stage II, recurrent, locally advanced or metastatic disease in members who are not eligible for any platinum containing chemotherapy
  - Subsequent therapy for stage II, recurrent, locally advanced or metastatic disease
  - Adjuvant therapy
  - 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
- Primary carcinoma of the urethra in any of the following settings:
  - Locally advanced, recurrent or metastatic disease for members who are not eligible for any platinum-containing chemotherapy
  - Recurrent or metastatic disease post-platinum or other chemotherapy
  - Adjuvant therapy
- Urothelial carcinoma of the upper genitourinary tract in any of the following settings:
  - Metastatic disease for members who are not eligible for any platinum-containing chemotherapy

  - Metastatic disease post-platinum or other chemotherapy
  - Adjuvant therapy if platinum-based neoadjuvant chemotherapy was given
- Urothelial carcinoma of the prostate in any of the following settings:
  - Metastatic disease for members who are not eligible for any platinum-containing chemotherapy
  - Metastatic disease post-platinum or other chemotherapy
  - Adjuvant therapy if platinum-based neoadjuvant chemotherapy was not given
- ~~Locally advanced or metastatic disease in members who are either:~~
  - ~~Not eligible for any platinum containing chemotherapy or~~
  - ~~Have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy~~
- ~~Bacillus Calmette Guerin (BCG) unresponsive, high risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors in members who will not undergo cystectomy~~

Authorization of 6 months may be granted in combination with enfortumab vedotin-ejfv for treatment of stage II, recurrent, locally advanced or metastatic urothelial carcinoma.

Solid Tumors

Authorization of 6 months may be granted as a single agent for treatment of solid tumors ~~in members 12 years of age or older~~ 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:

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

Colorectal Cancer

Authorization of 6 months may be granted as a single agent for the treatment of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

Appendiceal Neoplasms and Carcinoma

Authorization of 6 months may be granted as a single agent for the treatment of appendiceal neoplasms and carcinoma for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (TMB > 50 mut/Mb).

Small Bowel Adenocarcinoma

Authorization of 6 months may be granted as a single agent for neoadjuvant therapy or for the treatment of unresectable, medically inoperable, advanced or metastatic small bowel adenocarcinoma for microsatellite instability-high (MSI-H), or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (TMB > 50 mut/Mb).

Merkel Cell Carcinoma

Authorization of 6 months may be granted as a single agent for treatment of Merkel cell carcinoma in members ~~12 years of age or older~~ with ~~recurrent~~ locally advanced, regional, recurrent, or metastatic disease.

Gastric Cancer

Authorization of 6 months may be granted:

- For treatment of gastric adenocarcinoma in members who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease when any of the following criteria is met:
  - The requested medication will be used as subsequent therapy as a single agent for microsatellite instability-high (MSI-H), or deficient mismatch repair (dMMR), or tumor mutational burden (TMB) high (≥10 mutations/megabase (mut/Mb)) tumors.
  - The requested medication will be used as first line therapy as a single agent or in combination with chemotherapy for microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.
  - The requested medication will be used as first-line therapy in combination with trastuzumab and chemotherapy for HER2 overexpression positive disease with PD-L1 ≥ 1.
  - The requested medication will be used as first-line therapy in combination with chemotherapy for the first-line treatment of HER2-negative disease with PD-L1 ≥ 1.
- For treatment of gastric adenocarcinoma in members who are medically fit for surgery when any of the following criteria are met:
  - The requested medication will be used as a single agent or in combination with chemotherapy to treat microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) tumors.
  - The requested medication will be used as primary treatment in combination with trastuzumab and chemotherapy for surgically unresectable locoregional disease that is HER2 overexpression positive and PD-L1 ≥ 1.
  - The requested medication will be used as primary treatment in combination with chemotherapy for surgically unresectable locoregional disease that is HER2 overexpression negative with PD-L1 tumor expression by CPS ≥ 1.

~~for first-line treatment of locally advanced unresectable or metastatic gastric or gastroesophageal (GEJ) adenocarcinoma whose tumors express PD-L1 (CPS ≥ 1) in any of the following regimens:~~

- ~~In combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy for HER2 positive disease~~
- ~~In combination with fluoropyrimidine- and platinum-containing chemotherapy for HER2-negative disease~~

Esophageal Cancer and Esophagogastric Junction (EGJ) Cancer

Authorization of 6 months may be granted:

- In combination with platinum and fluoropyrimidine-based chemotherapy for treatment of esophageal and EGJ cancer with PD-L1 tumor expression by CPS ≥ 1 in members who are surgical candidates.
- As a single agent or in combination with platinum and fluoropyrimidine-based chemotherapy 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 (MSI-H) or deficient mismatch repair (dMMR) tumors.
- 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 criteria is met:
  - 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.

- 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 (MSI-H) or deficient mismatch repair (dMMR) tumors.
- The requested medication will be used as single agent subsequent therapy for squamous cell carcinoma with PD-L1 tumor expression by CPS ≥ 10.
- The requested medication will be used as first-line therapy in combination with platinum and fluoropyrimidine-based chemotherapy for squamous cell carcinoma or HER2 overexpression negative adenocarcinoma with PD-L1 tumor expression by CPS ≥ 1.
- The requested medication will be used as first-line therapy in combination with trastuzumab and platinum and fluoropyrimidine-based chemotherapy for HER2 overexpression positive adenocarcinoma with PD-L1 tumor expression by CPS ≥ 1.

~~for treatment of locally advanced or metastatic esophageal or gastroesophageal (GEJ) carcinoma that is not amenable to surgical resection or definitive chemoradiation in any of the following regimens:~~

- ~~In combination with platinum and fluoropyrimidine-based chemotherapy in tumors expressing PD-L1 (CPS ≥ 1)~~
- ~~As a single agent in tumors expressing PD-L1 (CPS ≥ 10) after at least one prior line of systemic therapy and squamous cell histology~~

Cervical Cancer

Authorization of 6 months may be granted for the treatment of cervical cancer in any of the following settings ~~regimens~~:

- Persistent, recurrent or metastatic disease in combination with chemotherapy with or without bevacizumab in members whose tumors express PD-L1 (CPS ≥1).
- Recurrent or metastatic disease as single agent or in combination with tisotumab vedotin-tftv subsequent therapy in members whose tumors express PD-L1 (CPS ≥1) or are microsatellite instability-high or mismatch repair deficient.
- FIGO stage III-IVA disease in combination with chemoradiation.
- ~~In combination with chemotherapy with or without bevacizumab for persistent, recurrent or metastatic tumors expressing PD-L1 (CPS ≥1)~~
- ~~As a single agent for recurrent or metastatic tumors expressing PD-L1 (CPS ≥1) with disease progression on or after chemotherapy~~
- ~~In combination with chemoradiotherapy (CRT) for FIGO 2014 stage III-IVA disease~~

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, or malignant germ cell tumors 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]).
- In combination with oral cyclophosphamide and bevacizumab for treatment of recurrent or persistent 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.
- As subsequent treatment for platinum-resistant or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, carcinosarcoma (malignant mixed Mullerian tumors), mucinous neoplasms of the

ovary, grade 1 endometrioid carcinoma, low-grade serous carcinoma, when the requested agent is used in combination with paclitaxel, with or without bevacizumab and the tumor is PD-L1 positive (CPS ≥1)
- As a single agent for progressive or recurrent small cell carcinoma of the ovary (hypercalcemic type)

UVEAL MELANOMA

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

Endometrial Carcinoma

Authorization of 6 months may be granted ~~in any of the following regimens~~:
- In combination with lenvatinib for treatment of advanced, metastatic, or recurrent endometrial carcinoma when either ~~both~~ of the following criteria are met:
  - The disease is mismatch repair proficient (pMMR) ~~or not MSI-H~~
  - The disease is mismatch repair deficient (dMMR) and has progressed following prior platinum-based chemotherapy
- 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.
- For treatment of endometrial carcinoma in combination with carboplatin and paclitaxel and continued as single agent maintenance therapy (for up to 20 cycles total) in members with stage III-IV or recurrent disease.
  - ~~The member has disease progression following prior systemic therapy and is not a candidate for curative surgery or radiation~~
  - ~~As a single agent for treatment of advanced endometrial carcinoma when both of the following criteria are met:~~
  - ~~The disease is dMMR or MSI-H~~
  - ~~The member has disease progression following prior systemic therapy and is not a candidate for curative surgery or radiation~~
- ~~In combination with carboplatin and paclitaxel and continued as a single agent (for up to 20 cycles total) for primary advanced or recurrent endometrial carcinoma~~

Anal Carcinoma

Authorization of 6 months may be granted for the treatment of anal carcinoma when the requested medication will be used in either of the following settings:
- In combination with paclitaxel and carboplatin for treatment of recurrent or metastatic disease.
- As a single agent for subsequent treatment of metastatic disease.

CNS Brain Metastases

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

Biliary Tract Cancers

Authorization of 6 months may be granted: ~~in combination with gemcitabine and cisplatin for locally advanced unresectable or metastatic biliary tract cancers.~~

- In combination with gemcitabine and cisplatin or carboplatin for locally advanced unresectable, resected gross residual (R2) disease or metastatic biliary tract cancers.
- As a single agent for unresectable, resected gross residual (R2) disease, or metastatic biliary tract cancers, including intrahepatic and extrahepatic cholangiocarcinoma and gallbladder cancer that is microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden high (TMB-H) [≥ 10 mut/Mb].
- For neoadjuvant treatment of resectable locoregionally advanced gallbladder cancer that does not present as jaundice when either of the following criteria are met:
  - The requested medication will be used in combination with cisplatin or carboplatin and gemcitabine.
  - The requested medication will be used as a single agent and member has microsatellite instability-high (MSI-H) and/or mismatch repair deficient (dMMR) tumors.

Hepatocellular Carcinoma

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

- The member has disease secondary to hepatitis B and has received prior systemic therapy other than a PD-1/PD-L1- containing regimen and will use the requested medication as a single agent.
- The requested medication will be used as single agent subsequent therapy.

~~secondary to hepatitis B in members who have received prior systemic therapy other than a PD-1/PD-L1-containing regimen and will use the requested medication as a single agent.~~

Vulvar Cancer

Authorization of 6 months may be granted for treatment of advanced, recurrent or metastatic vulvar cancer when any of the following criteria is met:

- The requested medication will be used as single agent subsequent therapy
- The requested medication will be used in combination with chemotherapy with or without bevacizumab.

Renal Cell Carcinoma

Authorization of 6 months may be granted for treatment of renal cell carcinoma in any of the following regimens:

- In combination with axitinib or lenvatinib for first-line treatment of advanced disease
- 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.

Thymic Carcinoma

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

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:

- Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor).

- Member has high-risk disease.

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.

Soft Tissue Sarcoma

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

- 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).
- The requested medication will be used as a single agent for the treatment of cutaneous angiosarcoma or dedifferentiated liposarcoma.
- The requested medication will be used as a single agent for the subsequent treatment of advanced/metastatic extremity/body wall sarcoma, head/neck sarcoma, or pleomorphic rhabdomyosarcoma.
- The requested medication will be used as a single agent for the subsequent treatment of unresectable, progressive, or stage IV retroperitoneal/intra-abdominal sarcoma.
- The requested medication will be used as neoadjuvant therapy in combination with radiation therapy, followed by single agent adjuvant therapy, for undifferentiated pleomorphic sarcoma (UPS) related sarcomas.

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 (MSI-H) or mismatch repair deficient (dMMR) tumors or tumor mutational burden-high (TMB-H) (≥10 mutations/megabase (mut/Mb) tumors).

Breast Cancer

- Authorization of 6 months may be granted for treatment of locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) when all of the following criteria are met:
  - The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
    - Human epidermal growth factor receptor 2 (HER-2)
    - Estrogen
    - Progesterone
  - Tumor must express PD-L1 (CPS ≥10)
  - The requested medication will be used in combination with sacituzumab govitecan-hziy (Trodelvy) or chemotherapy
- 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:
  - The diagnosis of triple-negative breast cancer is confirmed by the cancer cells testing negative for ALL of the following receptors:
    - Human epidermal growth factor receptor 2 (HER-2)
    - Estrogen
    - Progesterone

- The requested medication will be used as neoadjuvant treatment in combination with chemotherapy and continued as single agent adjuvant treatment after surgery

Prostate Cancer

Authorization of 6 months may be granted as a single agent for treatment of castration-resistant distant metastatic prostate cancer in members with tumor mutational burden (TMB) ≥10 mutations/megabase tumors.

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.

Vaginal Cancer

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

- The requested medication will be used in combination with cisplatin or carboplatin, paclitaxel, and with or without bevacizumab for recurrent or metastatic PD-L1 positive (CPS ≥1) disease.
- The requested medication will be used as single agent subsequent treatment for recurrent or metastatic disease that is PD-L1 positive or disease with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors.

~~Malignant~~ Pleural or Peritoneal Mesothelioma

Authorization of 6 months may be granted for first-line treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma~~, unresectable advanced or metastatic malignant pleural mesothelioma~~ when used in combination with pemetrexed and platinum chemotherapy.

Penile Cancer

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

- The requested medication will be used as first-line therapy in combination with fluorouracil and either cisplatin or carboplatin followed by single agent maintenance therapy for recurrent or metastatic disease.
- The requested medication will be used as single agent subsequent therapy for unresectable or metastatic disease with microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or tumor mutational burden-high (TMB-H ≥ 10 mut/Mb) tumors.

Chordoma

Authorization of 6 months may be granted for the treatment of recurrent conventional chordoma as a single agent.

CONTINUATION OF THERAPY

Adjuvant treatment of melanoma, HNSCC, TNBC, RCC, ~~or~~ NSCLC, or urothelial carcinoma

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, HNSCC, TNBC, RCC, ~~or~~ NSCLC or urothelial carcinoma who have not experienced disease recurrence or unacceptable toxicity.

NSCLC, HNSCC, MSI-H or dMMR cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, TNBC, TMB-H cancer, biliary tract cancer, pleural or peritoneal mesothelioma, penile cancer, chordoma ~~MPM~~

Authorization of 6 months may be granted (up to 24 months of continuous use) for continued treatment in members requesting reauthorization for NSCLC, HNSCC, MSI-H or dMMR cancers, gastric cancer, esophageal cancer, cervical cancer, HCC, MCC, RCC, endometrial carcinoma, cSCC, TNBC,TMB-H cancer, biliary tract cancer, pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes, penile caner, and chordoma ~~and malignant pleural mesothelioma~~ who have not experienced disease progression or unacceptable toxicity.

Urothelial Carcinoma ~~Cancer~~

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~~:

- 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.
- 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:
  - Member has not experienced disease progression or unacceptable toxicity.
  - For high-risk BCG-unresponsive non-muscle invasive bladder cancer only: disease is not persistent or recurrent.

All other indications ~~Unresectable or Metastatic Cutaneous Melanoma~~

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for an indication listed in the coverage criteria section ~~unresectable or metastatic cutaneous melanoma~~ who have not experienced disease progression or an unacceptable toxicity.

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

1. Keytruda Qlex [package insert]. Rahway, NJ: Merck Sharp & Dohme LLC; February 2026.
2. The NCCN Drugs & Biologics Compendium® © 2026 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org. Accessed March 16, 2026.
3. Makker V, Colombo N, Casado Herraez A, et al: Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. N Engl J Med 2022; 386(5):437-448.

EFFECTIVE DATE

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