Draft New Policy: Do Not Implement

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, 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, 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.

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, 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 or ALK 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 adjuvant treatment following complete resection of stage IIB, IIC, or III disease as a single agent in members 12 years of age or older.

Non-small Cell Lung Cancer (NSCLC)

Authorization of 6 months may be granted:

- 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, and then continued as single agent adjuvant therapy after surgery
- As adjuvant treatment as a single agent 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 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 Cancer

Authorization of 6 months may be granted as a single agent for treatment of urothelial cancer that is either of the following:

- 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 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.

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 or metastatic disease.

Gastric Cancer

Authorization of 6 months may be granted 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

Authorization of 6 months may be granted 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 regimens:

- 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

Endometrial Carcinoma

Authorization of 6 months may be granted in any of the following regimens:

- In combination with lenvatinib for treatment of advanced endometrial carcinoma when both of the following criteria are met:
  - The disease is mismatch repair proficient (pMMR) or not MSI-H
  - 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

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.

Hepatocellular Carcinoma

Authorization of 6 months may be granted for treatment of hepatocellular carcinoma 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.

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.

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.

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 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

Malignant Pleural Mesothelioma

Authorization of 6 months may be granted for first-line treatment of unresectable advanced or metastatic malignant pleural mesothelioma when used in combination with pemetrexed and platinum chemotherapy.

CONTINUATION OF THERAPY

Adjuvant Treatment of Melanoma, 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, TNBC, RCC or NSCLC 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, 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, and malignant pleural mesothelioma who have not experienced disease progression or unacceptable toxicity.

Urothelial 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:

- 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.

Unresectable or Metastatic Cutaneous Melanoma

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

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

Draft New Policy: Do Not Implement

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; September 2025.

EFFECTIVE DATE

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