09-J2000-22

Original Effective Date:11/15/14

Reviewed: 10/08/25

Revised: 04/01/26

Subject: Pembrolizumab (Keytruda®, Keytruda Qlex) Injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Pembrolizumab is a human monoclonal antibody that binds to the programmed death receptor (PD-1) on T-cells to block the interaction with PD-ligands, PD-L1 and PD-L2, on the tumor cell. The interaction of PD-1 with these ligands contributes to inhibition of active T-cell immune surveillance of tumors. Upregulation of PD-L1 occurs in some tumors and can further contribute to decreased immune response. Through binding of PD-1, pembrolizumab prevents inhibition of the anti-tumor immune response.

Pembrolizumab (Keytruda) was initially approved by the U.S. Food and Drug Administration (FDA) in September 2014 for the treatment of unresectable or metastatic melanoma. Pembrolizumab was later granted approval for the treatment of patients with either metastatic non-small cell lung cancer (NSCLC) or cervical cancer as a single agent or in combination with chemotherapy. The single agent use is approved for patients whose tumors express programmed death ligand 1 (PD-L1) with a Tumor Proportion Score (TPS) greater than or equal to 1%.A companion diagnostic test was approved to detect PD-L1 expression in non-small cell lung tumors. Pembrolizumab has also been FDA-approved for patients with Classical Hodgkin Lymphoma, cervical cancer, cutaneous squamous cell carcinoma, endometrial carcinoma, esophageal cancer, gastric cancer, hepatocellular carcinoma, Merkel cell carcinoma, primary mediastinal large B-cell lymphomas, renal cell cancer, squamous cell carcinoma of the head and neck, triple negative breast cancer, tumor mutational burden-high (TMB-H) solid tumors, locally advanced or metastatic urothelial carcinoma, unresectable or metastatic microsatellite instability high (MSI-H) solid tumors or colorectal cancer, and adjuvant treatment of melanoma. Many indications have been approved under accelerated approval based on tumor response rate and durability of response; continued approval is contingent upon results in confirmatory trials. A subcutaneous

administered formulation of pembrolizumab is available in combination with berahyaluronidase alfa-phph (Keytruda Qlex).

National Comprehensive Cancer Network (NCCN) Guidelines recommend pembrolizumab for the treatment of adrenocortical carcinoma, ampullary adenocarcinoma, appendiceal adenocarcinoma, anal cancer, bile duct cancer, bladder cancer, breast cancer, cervical cancer, brain metastases, bone cancer, Classical Hodgkin Lymphoma, colon and rectal cancer, Diffuse Large B-cell Lymphoma, endometrial carcinoma, esophageal and esophagogastric junction cancer, Extranodal NK/T-cell lymphomas, gallbladder cancer, gastric cancer, Gestational Trophoblastic Neoplasia, head and neck cancer, kidney cancer, melanoma, Merkel Cell carcinoma, mycosis fungoides/sezary syndrome, neuroendocrine tumors, non-small cell lung cancer, occult primary tumors, ovarian cancer, pancreatic cancer, pediatric diffuse high-grade gliomas, penile cancer, primary cutaneous CD30+ T-cell lymphoproliferative disorders, primary mediastinal large B-cell lymphomas, prostate cancer, small bowel adenocarcinoma, small cell lung cancer, soft tissue sarcomas, squamous cell skin cancer, testicular cancer, thymic carcinomas, thyroid cancer, uterine cancer, uveal melanoma, and vulvar cancer.

POSITION STATEMENT:

Initiation of pembrolizumab (Keytruda, Keytruda Qlex) **meets the definition of medical necessity** for members when **ALL** of the following are met:

I. **ONE** of the following to support clinical use is met:
   A. **ALL** of the following are met regarding FDA labeling or NCCN Compendium:
      i. **ONE** of the following (indication and usage):
         1. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) **AND** member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
         2. Indication is recognized in NCCN Drugs and Biologics Compendium **AND** usage as a Category 1 or 2A recommendation (Table 1).
      ii. **ONE** of the following (diagnostic testing¶):
         1. **ALL** of the following:
            a. The requested indication requires genetic/specific diagnostic testing per FDA labeling or NCCN Compendium for the requested agent
            b. Genetic/specific diagnostic testing has been completed
            c. The results of the genetic/specific diagnostic testing indicate therapy with the requested agent is appropriate.
         2. The requested indication does **NOT** require specific genetic/diagnostic testing per FDA labeling or NCCN Compendium.
   B. Requested product is designated as an orphan drug by the FDA for the requested indication **AND** the indication is not included in the FDA labeling or the NCCN compendium as a 1 or 2A recommendation (i.e., "Designated/Approved", "Designated") (Orphan drug designations can be found at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

C. The indication **AND** usage of the requested product is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article.

NOTE:

- Case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support for use.
- Clinical studies must be supportive of use for a similar patient population (e.g., indication, diagnosis, disease severity, genetic or tumor mutations) and for the intended treatment plan, including any concomitant therapy.

II. Pembrolizumab will be used as monotherapy with the following exceptions:

D. Combination therapy for the indication is supported by FDA labeling, NCCN Compendium, or standard reference compendia (Table 2)

E. Combination therapy for the indication is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article

i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

III. The dose does not exceed the maximum FDA-approved dose and frequency* with the following exceptions:

A. Dose and frequency for indication are supported by NCCN Compendium or standard reference compendia (Table 2)

B. Dose and frequency for indication are supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article

NOTE: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

Approval duration: 6 months

Continuation of pembrolizumab (Keytruda, Keytruda Qlex) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. The member has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage
2. Member's disease has not progressed during treatment with pembrolizumab
3. Pembrolizumab will be used as monotherapy with the following exceptions:

a. Combination therapy for the indication is supported by FDA labeling, NCCN Compendium, or standard reference compendia (Table 2)

b. Combination therapy for indication is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article

i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

4. The dose does not exceed the maximum FDA-approved dose and frequency with the following exceptions:
    a. Dose and frequency for the indication is supported by NCCN Compendium or standard reference compendia (Table 2)
    b. Dose and frequency for indication is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article
        i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

Approval duration: 1 year**

***NOTE**: The maximum FDA approved dose for pembrolizumab IV is 200 mg every 3 weeks or 400 mg every 6 weeks for adult patients and 2 mg/kg (up to 200 mg) every 3 weeks for pediatrics. The maximum FDA-approved dose for pembrolizumab/berahyaluronidase alfa-pmph subcutaneous is 395 mg/4,800 units every 3-weeks or 790 mg/9,600 units every 6-weeks.

**For adjuvant treatment of melanoma,adjuvant treatment of renal cell carcinoma, or adjuvant treatment of non-small cell lung cancer, the duration of therapy is 12 months. For neoadjuvant treatment of triple negative breast cancer, the duration of therapy is 24 weeks in combination with chemotherapy, followed by adjuvant treatment as a single agent for up to 27 weeks (approximately 12 months). For neoadjuvant treatment of resectable non-small cell lung cancer, the duration of therapy is 12 weeks in combination with chemotherapy, followed by adjuvant treatment after surgery as a single agent for up to 39 weeks (approximately 12 months).

† Includes incomplete resection.

FDA Companion Diagnostics: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Table 1

NCCN Categories of Evidence Consensus	
Category 1	Based upon high-level evidence; there is uniform NCCN consensus that the intervention is appropriate
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate
Category 2B	Based upon lower-level evidence, there NCCN consensus that the intervention is appropriate
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate

Table 2

Other compendia	
Compendium	**Covered Uses†**
AHFS-DI	Narrative text is supportive
Clinical Pharmacology	Narrative text is supportive

Lexicomp	Evidence rating A, B or G
Thomson Micromedex DrugDex	Meets requirements for **BOTH** of the following: • Strength of recommendation: Class I (Recommended) or IIa (Recommended, In Most Cases) • Efficacy: Class I (Effective) or IIa (Evidence Favors Efficacy)
†If covered use criteria are not met, the request should be denied. AHFS-DI, American Hospital Formulary Service Drug Information; For additional information regarding designated compendia, please refer to the "Definitions" section.	

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved

Keytruda

- Melanoma:
  - Treatment of unresectable or metastatic melanoma: 200 mg IV over 30 minutes every three weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression or unacceptable toxicity occurs. See Keytruda Qlex for subcutaneous administration.
  - Adjuvant treatment of Stage IIB, IIC, or III melanoma following complete resection: 200 mg IV over 30 minutes every three weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics 12 years of age and older (up to 200 mg). Continue treatment until disease recurrence, unacceptable toxicity, or up to 12 months. See Keytruda Qlex for subcutaneous administration.
- Non-Small Cell Lung Cancer as a single agent or in combination with chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Select patients for treatment based on the presence of positive PD-L1 expression for use as a single agent. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. For adjuvant treatment following resection and platinum-based chemotherapy for adults, continue until disease recurrence, unacceptable toxicity, or up to 12 months. For neoadjuvant treatment in combination with chemotherapy for 12 weeks or until dease progression that precludes definitive surgery or unacceptable toxicity followed by adjuvant treatment as a single agent after surgery for 39 weeks or until disease recurrence or unacceptable toxicity. See Keytruda Qlex for subcutaneous administration
- Malignant Pleural Mesothelioma (MPM) in combination with pemetrexed and platinum chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.

- Squamous cell carcinoma of the Head and Neck as a single agent or in combination with chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Select patients for treatment based on the presence of positive PD-L1 expression when used first line as a single agent. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Classical Hodgkin Lymphoma: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics (up to 200 mg). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
- Primary Mediastinal Large B-cell Lymphoma: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics (up to 200 mg). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.
- Urothelial carcinoma as a single agent or in combination with enfortumab vedotin: 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics (up to 200 mg). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- MSI-H or dMMR colorectal cancer: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Gastric cancer:
    - HER2-positive gastric cancer in combination with trastuzumab and chemotherapy: 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks) prior to trastuzumab and chemotherapy when given on the same day. Select patients for treatment based on the presence of positive PD-L1 expression. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
    - HER2-negative gastric cancer In combination with chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Select patients for treatment based on the presence of positive PD-L1 expression. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Esophageal cancer as a single agent or in combination with chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Select patients for treatment based on the presence of positive PD-L1 expression. If given in combination with chemotherapy, administer prior to chemotherapy when given on the same

day. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.

- Cervical cancer:
  - Single agent: 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks). Select patients for treatment based on the presence of positive PD-L1 expression. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
  - In combination with chemotherapy, with or without bevacizumab: 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks) prior to chemotherapy with or without bevacizumab when given on the same day. Select patients for treatment based on the presence of positive PD-L1 expression. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
  - In combination with chemoradiotherapy (CRT): 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks) prior to chemotherapy. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Hepatocellular cancer: 200 mg IV over 30 minutes every 3 weeks(dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Biliary tract cancer in combination with chemotherapy: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Merkel cell carcinoma: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics (up to 200 mg). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Renal cell carcinoma (RCC):
  - Treatment of advanced RCC in combination with either axitinib or lenvatinib: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks) with axitinib 5 mg orally twice daily or lenvatinib 20 mg once daily. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
  - Adjuvant treatment of patients with RCC at intermediate-high or high risk of disease recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions: 200 mg IV over 30 minutes every three weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease recurrence, unacceptable toxicity, or up to 12 months. See Keytruda Qlex for subcutaneous administration.

- Endometrial carcinoma:
    - In combination with carboplatin and paclitaxel, followed by pembrolizumab as a single agent: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
    - As a single agent or in combination with lenvatinib: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks) as a single agent for MSI-H or dMMR cancer. When used in combination with lenvatinib 20 mg orally once daily for mismatch repair proficient tumors (pMMR) or that are not MSI-H. Select patients for treatment based on MSI-H or dMMR status. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration
- Tumor mutational burden-high (TMB-H) cancer: 200 mg IV over 30 minutes every 3 weeks for adult patients (dosing alternative of 400 mg IV over 30 minutes every six weeks) and 2 mg/kg IV every 3 weeks for pediatrics (up to 200 mg). Select patients for treatment based on TMB-H (greater than or equal to 10 mutations/megabase) solid tumors. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Triple-negative breast cancer (TNBC):
    - Neoadjuvant and Adjuvant treatment of TNBC: neoadjuvant treatment in combination with chemotherapy for 24 weeks (8 doses of 200 mg every 3 weeks or 4 doses of 400 mg every 6 weeks) or until disease progression or unacceptable toxicity, followed by adjuvant treatment as a single agent for up to 27 weeks (9 doses of 200 mg every 3 weeks or 5 doses of 400 mg every 6 weeks) or until disease recurrence or unacceptable toxicity. See Keytruda Qlex for subcutaneous administration.
    - Locally recurrent unresectable or metastatic TNBC: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks) prior to chemotherapy when given on the same day. Select patients for treatment based on the presence of positive PD-L1 expression. Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.
- Cutaneous Squamous cell carcinoma: 200 mg IV over 30 minutes every 3 weeks (dosing alternative of 400 mg IV over 30 minutes every six weeks). Continue treatment until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. See Keytruda Qlex for subcutaneous administration.

Note: For members ≤ 50 kg, a dose of 2 mg/kg every 3 weeks may be used. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.

Keytruda Qlex:

For adults and pediatric patients 12 years and older weighing greater than 40 kg:

- **Every 3 week dosing**: 395 mg pembrolizumab and 4800 units berahyaluronidase alfa - inject 2.4 mL subcutaneously in the abdomen or thigh over 1 minute
- **Every 6 week dosing**: 790 mg pembrolizumab and 9600 units berahyaluronidase alfa - inject 4.8 mL subcutaneously in the abdomen or thigh over 2 minutes

Dose Adjustments

Keytruda

- Withhold pembrolizumab for any of the following (Grades per Common Terminology Criteria for Adverse Events):
    - Grade 2 pneumonitis
    - Grade 2 or 3 colitis
    - Grade 3 or 4 endocrinopathies
    - Grade 4 hematological toxicity in cHL patients
    - Grade 2 or 3 hypophysitis
    - Grade 3 hyperthyroidism
    - Grade 2 nephritis
    - Grade 3 severe skin reactions or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
    - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 3 and up to 5 times the upper limit of normal (ULN) or total bilirubin greater than 1.5 and up to 3 times the ULN
    - Any other severe Grade 3 treatment-related adverse reaction
- Resume pembrolizumab in patients whose adverse reactions recover to Grade 0-1.
- Permanently discontinue pembrolizumab for any of the following:
    - Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy, or hematological toxicity in patients with cHL)
    - Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
    - Grade 3 or 4 hypophysitis
    - Grade 3 or 4 hyperthyroidism
    - Grade 3 or 4 nephritis
    - Grade 4 severe skin reactions or confirmed Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)
    - AST or ALT greater than 5 times the ULN or total bilirubin greater than 3 times the ULN (for patients with liver metastasis, see prescribing information)
    - Grade 3 or 4 infusion-related reactions

- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks
- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after the last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

Drug Availability

Keytruda

- 50 mg, lyophilized powder in single-use vial for reconstitution
- 100 mg/4 mL (25 mg/mL) solution in a single-use vial

Keytruda Qlex

- 395 mg pembrolizumab and 4800 units berahyaluronidase alfa per 2.4 mL (165 mg/2000 units per mL) in a single-dose vial
- 790 mg pembrolizumab and 9600 units berahyaluronidase alfa per 4.8 mL (165 mg/2000 units per mL) in a single-dose vial

PRECAUTIONS:

Boxed Warning

None

Contraindications

Keytruda: None

Keytruda Qlex: contraindicated in patients with known hypersensitivity to berahyaluronidase alfa, hyaluronidase or to any of its excipients

Precautions/Warnings

- Immune-mediated adverse reactions: administer corticosteroids based on the severity of the reaction. See prescribing information for dose modifications and monitoring recommendations for immune-mediated reactions including: pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, thyroid disorders, type 1 diabetes mellitus) nephritis, skin reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis).
- Infusion-related reactions: stop infusion and permanently discontinue for severe or life-threatening reactions.
- Embryo-fetal toxicity: May cause fetal harm.
- Multiple myeloma: treatment in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

- Transplant recipients: Consider the risk of possible organ rejection in donor organ recipients. Also, complications of allogeneic HSCT may occur: Monitor for hepatic veno-occlusive disease, grade 3-4 acute GVHD including hyperacute GVHD, steroid-requiring febrile syndrome, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

J9271	Injection, pembrolizumab, 1 mg
J9277	Injection, pembrolizumab, 1 mg and berahyaluronidase alfa-pmph

ICD-10 Diagnosis Codes That Support Medical Necessity

C00.0 – C08.9	Malignant neoplasm of lip, base of tongue, of other and unspecified parts of tongue, gum, floor of mouth, palate, of other and unspecified parts of mouth, parotid and salivary gland.
C09.0 – C10.9	Malignant neoplasm of tonsil and oropharynx
C11.0 – C11.9	Malignant neoplasm of nasopharynx
C12.0 – C14.8	Malignant neoplasm of piriform sinus, hypopharynx and other and ill-defined sites in the lip, oral cavity and pharynx.
C15.3 – C15.9	Malignant neoplasm of esophagus
C16.0 – C16.9	Malignant neoplasm of stomach
C17.0 – C17.9	Malignant neoplasm of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.0 – C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.3	Angiosarcoma of liver
C22.8	Malignant neoplasm of liver, primary, unspecified
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0 – C24.9	Malignant neoplasm of other and unspecified parts of biliary tract
C25.0 – C25.9	Malignant neoplasm of pancreas
C30.0	Malignant neoplasm of nasal cavity
C31.0 – C31.9	Malignant neoplasm of accessory sinuses
C32.0 – C32.9	Malignant neoplasm of larynx
C33	Malignant neoplasm of trachea
C34.00 – C34.02	Malignant neoplasm of unspecified main bronchus
C34.10 – C34.12	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, unspecified bronchus or lung
C34.30 – C34.32	Malignant neoplasm of lower lobe, unspecified bronchus or lung

C34.80 – C34.82	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C37	Malignant neoplasm of thymus
C38.4	Malignant neoplasm of pleura
C40.00 – C40.92	Malignant neoplasm of bone and articular cartilage of limbs
C41.0 – C41.9	Malignant neoplasm of bone and articular cartilage of other and unspecified sites
C43.0 – C43.9	Malignant melanoma of skin
C4A.0 – C4A.9	Merkel cell carcinoma, unspecified
C44.00	Malignant neoplasm of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C44.121 – C44.1292	Squamous cell carcinoma of skin of unspecified eyelid, including canthus
C44.221 – C44.229	Squamous cell carcinoma of skin of unspecified ear and external auricular
C44.320	Squamous cell carcinoma of skin of unspecified parts of face
C44.321	Squamous cell carcinoma of skin of nose
C44.329	Squamous cell carcinoma of skin of other parts of face
C44.42	Squamous cell carcinoma of skin of scalp and neck
C44.520	Squamous cell carcinoma of anal skin
C44.521	Squamous cell carcinoma of skin of breast
C44.529	Squamous cell carcinoma of skin of other part of trunk
C44.621 – C44.629	Squamous cell carcinoma of skin of unspecified upper limb, including shoulder
C44.721 – C44.729	Squamous cell carcinoma of skin of unspecified lower limb, including hip
C44.82	Squamous cell carcinoma of overlapping sites of skin
C44.92	Squamous cell carcinoma of skin, unspecified
C46.0 – C46.9	Kaposi's sarcoma
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.8	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C50.011 – C50.929	Malignant neoplasm of breast
C51.0 – C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C58	Malignant neoplasm of placenta
C60.0 – C60.9	Malignant neoplasm of penis
C61	Malignant neoplasm of prostate
C62.00 – C62.92	Malignant neoplasm of testis
C63.7 – C63.8	Malignant neoplasm of overlapping sites and other male genital organs
C64.1 – C64.9	Malignant neoplasm of kidney, except renal pelvis

C65.1 – C65.9	Malignant neoplasm of renal pelvis
C66.1 – C66.9	Malignant neoplasm of ureter
C67.0 – C67.9	Malignant neoplasm of bladder
C68.0	Malignant neoplasm of urethra
C69.30 – C69.32	Malignant neoplasm of choroid
C69.40 – C69.42	Malignant neoplasm of ciliary body
C69.60 – C69.62	Malignant neoplasm of orbit
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye
C71.0 – C71.9	Malignant neoplasm of brain
C72.0 – C72.9	Malignant neoplasm of spinal cord and cauda equina
C73	Malignant neoplasm of thyroid gland
C74.00 - C74.92	Malignant neoplasm of adrenal gland
C7A.1	Malignant poorly-differentiated neuroendocrine tumors
C7A.8	Other malignant neuroendocrine tumors
C7B.00 – C7B.04	Secondary carcinoid tumors
C7B.1	Secondary Merkel cell carcinoma
C7B.8	Other secondary neuroendocrine tumors
C73	Malignant neoplasm of thyroid gland
C74.00 – C74.92	Malignant neoplasm of adrenal gland
C76.0	Malignant neoplasm of head, face and neck
C77.0	Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck
C78.00 – C78.89	Secondary malignant neoplasm of respiratory and digestive organs
C79.31	Secondary malignant neoplasm of brain
C79.51 – C79.52	Secondary malignant neoplasm of bone and bone marrow
C79.70 – C79.72	Secondary malignant neoplasm of adrenal gland
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
C79.9	Secondary malignant neoplasm of other unspecified site
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C81.10 – C81.99	Hodgkin Lymphoma
C82.00 – C82.99	Follicular Lymphoma
C83.90 – C83.99	Non-follicular (diffuse) lymphoma, unspecified
C84.00 – C84.19	Mycosis fungoides/Sezary disease
C84.Z0 – C84.Z9	Other mature T/NK-cell lymphomas
C84.90 – C84.99	Mature T/NK-cell lymphomas, unspecified
C85.10 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type
C86.60	Primary cutaneous CD30-positive T-cell proliferations
D09.0	Carcinoma in situ of bladder

D15.0	Benign neoplasm of thymus
D37.01 – D37.09	Neoplasm of uncertain behavior of oral cavity and digestive organs
D37.1 – D37.9	Neoplasm of uncertain behavior of digestive organs
D38.0	Neoplasm of uncertain behavior of larynx
D38.4	Neoplasm of uncertain behavior of thymus
D38.5	Neoplasm of uncertain behavior of other respiratory organs
D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
D39.2 – D39.9	Neoplasm of uncertain behavior of placenta, other female genital organs
O01.9	Hydatidiform mole, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled POSITION STATEMENT.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

Medicare Advantage: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

ALK gene rearrangements – The anaplastic lymphoma kinase (ALK) fusion oncogene is a predictive biomarker that has been identified in a subset of patients with NSCLC. Presence of the ALK arrangement is predictive of treatment benefit with ALK targeted therapies.

EGFR mutation – The presence of the epithelial growth factor receptor (EGFR) mutation (exon 19 deletion or exon 21 L858R mutation) is predictive of treatment benefit from EGFR tyrosine kinase inhibitor therapy

PD-L1 – Cytotoxic T-cell inhibition occurs when binding of the programmed death 1 (PD-1) receptor to one of its ligands: ligand 1 (PD-L1) or 2 (PD-L2). Upregulation of PD-L1 occurs in some tumors and can inhibit active T-cell surveillance of tumors. Presence of the PD-L1 biomarker in tumor cells may be predictive of treatment benefit with PD-1 inhibitors.

RELATED GUIDELINES:

Carboplatin (Paraplatin®) IV, 09-J0000-93
Dabrafenib (Tafinlar®) Capsules, 09-J2000-00
Ipilimumab (Yervoy™) IV, 09-J1000-34
Nivolumab (Opdivo®), 09-J2000-33
Trametinib (Mekinist™) Tablets, 09-J1000-99
Vemurafenib (Zelboraf™), 09-J1000-40

OTHER:

Table 3: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 4: Karnofsky Performance Status (KPS) (%)

	Score	Description
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

progressing rapidly.		

Table 5: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

Table 6: Child-Pugh Score and Classification

	1 point	2 points	3 points
Total bilirubin	< 2	2-3	> 3
Serum albumin	> 3.5	2.8-3.5	< 2.8
INR	> 1.7	1.71-2.20	< 2.20
Ascites	None	Mild	Severe
Hepatic encephalopathy	None	Grade I-II	Grade III-IV
Classification of Result: Class A: 5-6 points Class B: 7-9 points Class C: 10-15 points			

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2025 [cited 2025 Sept 30]. Available from: http://www.clinicalpharmacology.com/.
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3. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2025 Sept 30].
4. Keytruda (pembrolizumab) injection [package insert]. Merck Sharp and Dohme Corp. Whitehouse Station, NJ. August 2025.
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6. National Cancer Institute. Common Terminology Criteria for Adverse Events. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Accessed 9/24/15.

7. National Comprehensive Cancer Network (NCCN). Drugs & Biologics Compendium [Internet]. Fort Washington (PA): National Comprehensive Cancer Network.Available from: http://www.nccn.org/professionals/drug_compendium/content/contents.asp/. Accessed 10/02/25
8. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration.Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/. Accessed 10/02/25.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 10/08/25.

GUIDELINE UPDATE INFORMATION:

11/15/14	New Medical Coverage Guideline.
06/15/15	Revision to guidelines; consisting of description and position statement and references
07/15/15	Revision to guidelines; updated HCPCS codes
08/15/15	Revision to guidelines; consisting of position statement.
11/15/15	Revision to guideline; consisting of updating position statement, dosing/administration, warnings/precautions, definitions, coding, and references
12/15/15	Revision to guideline; consisting of updating position statement, description and references.
01/01/16	Annual HCPCS coding update: added code J9271 and deleted codes C9027 and J9999.
6/15/16	Revision to guideline; consisting of updating position statement, description, coding and references.
7/15/16	ICD-10 coding update.
8/15/16	Revision to guideline; consisting of updating position statement and references.
9/15/16	Revision to guideline; consisting of updating description, position statement, dosing, warnings, coding and references.
10/15/16	Revision to guideline; consisting of updating position statement and references.
11/15/16	Revision to guideline; consisting of updating position statement, coding, and references.
12/15/16	Revision to guideline; consisting of updating position statement, description, dosing, coding and references.
02/15/17	Review and revision to guideline; consisting of updating position statement, description, coding and references.
04/15/17	Revision to guideline; consisting of updating position statement and references.
05/15/17	Revision to guideline; consisting of updating the position statement and references.
07/15/17	Review and revision to guideline; consisting of updating position statement, description, dosing, coding and references.
09/15/17	Review and revision to guideline; consisting of updating position statement, description, coding and references.
10/15/17	Revision to guideline; consisting of updating position statement, description, coding and references.

11/15/17	Revision to guideline; consisting of updating position statement, description, coding and references.
12/15/17	Revision to guideline; consisting of updating position statement, description, coding and references.
01/15/18	Revision to guideline; consisting of updating position statement, description, coding and references.
02/15/18	Revision to guideline; consisting of updating position statement, coding and references.
03/15/18	Revision to guideline; consisting of updating position statement, coding and references.
04/15/18	Review and revision to guideline; consisting of updating position statement, description, coding and references
05/15/18	Revision to guideline; consisting of updating position statement, coding and references.
06/15/18	Revision to guideline; consisting of updating position statement, coding and references.
07/15/18	Revision to guideline; consisting of updating position statement, dosing, coding, and references.
08/15/18	Revision to guideline; consisting of updating position statement and references.
12/15/18	Revision to guideline; consisting of updating position statement, description, dosing and references.
02/15/19	Revision to guideline; consisting of updating position statement, description, dosing and references.
05/15/19	Review and revision to guideline; consisting of updating position statement and references.
06/15/19	Revision to guideline; consisting of updating position statement, description and references.
07/15/19	Revision to guideline; consisting of updating position statement and references.
09/15/19	Revision to guideline; consisting of updating position statement, dosing and references.
12/15/19	Revision to guideline; consisting of updating position statement, dosing and references.
02/15/20	Revision to guideline; consisting of updating position statement and references.
05/15/20	Revision to guideline; consisting of updating position statement and references.
06/15/20	Revision to guideline; consisting of updating position statement, dosing and references.
08/15/20	Review and revision to guideline; consisting of updating position statement, description, dosing, coding and references.
01/15/21	Revision to guideline; consisting of updating the position statement, coding, and references.
04/15/21	Revision to guideline; consisting of updating the position statement and references.
05/15/21	Revision to guideline; consisting of updating the position statement and references.
09/15/21	Revision to guideline; consisting of updating the position statement, dosing, and references.
11/15/21	Revision to guideline; consisting of updating the position statement, dosing, and references.
01/15/22	Revision to guideline; consisting of updating the position statement, dosing, and references.

11/15/22	Review and revision to guideline; consisting of updating the position statement to include review of FDA label and NCCN 1 or 2A indications. Update to description, dosing, coding, and references.
01/15/23	Revision to guideline; including updating coding and references.
02/15/24	Review and revision to guideline; including updating dosing, coding, and references.
10/01/24	ICD-10 coding, dosing, and reference update.
03/15/25	Review and revision to guideline; including updating dosing and references.
11/15/25	Review and revision to guideline; including the addition of Keytruda Qlex to the position statement and updating dosing, coding, and references.
04/01/26	Revision: Added HCPCS code J9277 and removed code J9999.