MEDICAL MUTUAL®

Drug Policy

Policy:	**201430-CC**	**Initial Effective Date: 12/30/2014**
Code(s):	**HCPCS J9271**	**Annual Review Date: 01/22/2019**
SUBJECT:	**Keytruda® (pembrolizumab for injection, intravenous use)**	**Last Revised Date: 01/22/2019**

Prior approval is required for some or all procedure codes listed in this Corporate Drug Policy.

OVERVIEW

Keytruda, a human programmed death receptor-1 (PD-1) blocking antibody, is indicated for the treatment of the following indications:[1]

1) Melanoma, for the treatment of patients with unresectable or metastatic disease; AND
2) Non-small cell lung cancer (NSCLC), in the following situations:
   a. As a single agent for the first-line treatment of patients with metastatic disease whose tumors have high programmed death-ligand 1 (PD-L1) expression (tumor proportion score [TPS] ≥ 50%) as determined by an FDA-approved test, with no epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*) genomic tumor aberrations; AND
   b. As a single agent for the treatment of patients with metastatic disease whose tumors express PD-L1 (TPS ≥ 1%) as determined by an FDA-approved test and 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; AND
   c. In combination with Alimta® (pemetrexed intravenous injection) and platinum-based chemotherapy, for the first-line treatment of patients with metastatic disease with no EGFR or ALK genomic tumor aberrations; AND
   d. In combination with carboplatin and either paclitaxel or Abraxane® (nab-paclitaxel injection), for first-line treatment in metastatic squamous NSCLC; AND
3) Head and neck squamous cell carcinoma (HNSCC), for the treatment of recurrent or metastatic disease with disease progression on or after platinum-containing chemotherapy;* AND
4) Classical Hodgkin lymphoma (cHL), treatment of adult and pediatric patients with refractory disease, or who have relapsed after three or more prior lines of therapy;* AND
5) Primary mediastinal large B-cell lymphoma (PMBCL), treatment of adult and pediatric patients with refractory disease, or who have relapsed after two or more prior line of therapy;* AND

   Limitation of Use: Keytruda is not recommended for treatment of patients with PMBCL who require urgent cytoreductive therapy.
6) Urothelial carcinoma, in the following situations:

a. Treatment locally advanced or metastatic disease in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status;* OR
b. Treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; AND

7) Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), treatment of adult and pediatric patients with unresectable or metastatic disease, in the following situations:
   - solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options;* OR
   - colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan;* AND

   Limitation of Use: The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system (CNS) cancers have not been established.
8) Gastric cancer, treatment of patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction (GEJ) adenocarcinoma whose tumors express PD-L1 (Combined Positive Score [CPS] ≥ 1) as determined by an FDA-approved test, with disease progression on or after two or more lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, human epidermal growth factor receptor 2 (HER2)/neu-targeted therapy;* AND
9) Cervical cancer, treatment of patients with recurrent or metastatic disease with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test;* AND
10) Hepatocellular carcinoma, treatment of patients who have been previously treated with Nexavar® (sorafenib tablets);*
11) Merkel cell carcinoma, for adults and pediatric patients with recurrent, locally advanced, or metastatic disease.*

*This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The recommended dose of Keytruda is 200 mg (for pediatric patients, 2 mg/kg up to 200 mg) administered as an intravenous infusion once every 3 weeks. It is given until disease progression or unacceptable toxicity, (or up to 24 months in patients with non-melanoma indications without disease progression). There are no recommended dose reductions in the prescribing information. Management of adverse events may require that Keytruda be withheld or permanently discontinued as determined by the prescribing physician.

POLICY STATEMENT

Prior authorization is recommended for medical benefit coverage of Keytruda. Approval is recommended for those who meet the Criteria and Dosing for the listed indication(s). Requests for doses outside of the established dosing documented in this policy will be considered on a case-by-case basis by an Express Scripts clinician (i.e., Medical Director or

Pharmacist). All approvals are provided for the duration noted below. In cases where the approval is authorized in months, 1 month is equal to 30 days.

Because of the specialized skills required for evaluation and diagnosis of patients treated with Keytruda as well as the monitoring required for adverse events (AEs) and long-term efficacy, initial approval requires Keytruda to be prescribed by or in consultation with a physician who specializes in the condition being treated.

RECOMMENDED AUTHORIZATION CRITERIA

Coverage of Keytruda is recommended in those who meet one of the following criteria:

FDA-Approved Indications

1. **Cervical Cancer.** Approve for 6 months if the patient meets ALL of the following (A, B, and C):
   - **A)** The patient has tried chemotherapy (e.g., cisplatin, paclitaxel, Avastin [bevacizumab intravenous injection], topotecan, carboplatin); AND
   - **B)** The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND
   - **C)** Keytruda is prescribed by or in consultation with an oncologist.

   Note: Also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

   Dosing. Approve if the dose is 200 mg as an intravenous infusion administered once every 3 weeks.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

2. **Classic Hodgkin Lymphoma (cHL).** Approve for 6 months if the patient meets BOTH of the following (A and B):
   - A. ONE the following conditions apply (i, ii, or iii):
     - i. The patient has had a hematopoietic stem cell transplantation (HSCT); OR
     - ii. The patient has tried three or more systemic regimens (e.g., ABVD [doxorubicin, bleomycin, vinblastine, and dacarbazine], Sanford V [doxorubicin, vinblastine, mechlorethamine, etoposide, vincristine, bleomycin, and prednisone], escalated BEACOPP [bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone]) AND this includes an auto-HSCT as one line of therapy; OR
     - iii. The patient is not eligible for transplant according to the prescribing physician; AND
   - B. Keytruda is prescribed by or in consultation with an oncologist.

   Dosing. Approve the following dosing regimens:

A) 200 mg as an intravenous infusion given once every 3 weeks; OR
B) 2 mg per kg (up to a maximum of 200 mg) given as an intravenous infusion given once every 3 weeks.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
- Treatment may continue until disease progression or unacceptable toxicity.

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3. **Gastric Cancer, Gastroesophageal Junction (GEJ) Cancer, or Esophageal Cancer.** Approve for 6 months if the patient meets ALL of the following (A, B, C, and D):
   a) The patient's tumor expression for programmed death-ligand 1 (PD-L1) as determined by an approved test has a combined positive score (CPS) ≥ 1; AND
   b) The patient has tried therapy with a fluoropyrimidine (e.g., 5-fluorouracil [5-FU], capecitabine) and platinum (e.g., cisplatin, carboplatin); AND
   c) If the patient's tumor is human epidermal growth factor receptor 2 (HER2) or HER2/neu positive, targeted therapy with trastuzumab intravenous infusion (Herceptin®) has been tried; AND
   d) Keytruda is prescribed by or in consultation with an oncologist.

   Note: also see **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.**

   Dosing. Approve if the dose is 200 mg as an intravenous infusion given once every 3 weeks.[1,28-29]

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

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4. **Head and Neck Squamous Cell Carcinoma (HNSCC).** Approve for 6 months if the patients meets BOTH of the following (A and B):
   ~~A.~~ The patient meets ONE of the following conditions (i or ii):
      i. The patient has tried chemotherapy (e.g., cisplatin, carboplatin, Erbitux® [cetuximab intravenous infusion], 5-fluorouracil [5-FU], capecitabine, paclitaxel, docetaxel, methotrexate [MTX]); OR
      ii. A platinum-containing chemotherapy regimen or other chemotherapy is contraindicated, according to the prescribing physician; AND
   B. Keytruda is prescribed by or in consultation with an oncologist.

   Dosing. Approve if the dose is 200 mg as an intravenous infusion given once every 3 weeks.[1]

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).

- Treatment may continue until disease progression or unacceptable toxicity.

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5. **Hepatocellular Carcinoma, Including Hepatobilicary Cancers**. Approve for 6 months if the patient meets the following conditions (A and B):
   A. The patient has tried at least one tyrosine kinase inhibitor (TKI) [e.g., Nexavar {sorafenib tablets}, Lenvima {levatinib capsules}]; AND
   B. Keytruda is prescribed by or in consultation with an oncologist.

   Dosing. Approve if the dose is 200 mg as an intravenous infusion given every 3 weeks.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

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6. **Melanoma** [NOTE: This includes cutaneous melanoma, brain metastases due to melanoma and uveal melanoma]. Approve for 6 months if the patient meets ALL of the following (A, B, and C):
   A. The patient meets ONE of the following (i or ii):
      i. The patient has unresectable, advanced, or metastatic melanoma; OR
      ii. Keytruda will be used as adjuvant treatment (e.g., in a patient with no evidence of disease following resection of node-positive disease, locoregional recurrence, or in transit recurrence); AND
   B. Keytruda will not be used in combination with Yervoy® (ipilimumab intravenous infusion); AND
   C. Keytruda is prescribed by or in consultation with an oncologist.

   Dosing. Approve if the dose is 200 mg as an intravenous infusion given once every 3 weeks.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

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7. **Merkel Cell Carcinoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A. The patient has recurrent, locally advanced, or metastatic disease; AND
   B. Keytruda is prescribed by or in consultation with an oncologist.

   Dosing. Approve the following dosing regimens:

A) 2 mg/kg (up to 200 mg) as an intravenous infusion given once every 3 weeks; OR
B) 200 mg as an intravenous infusion given once every 3 weeks.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
- Treatment may continue until disease progression or unacceptable toxicity.

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8. **Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Solid Tumors.** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A) One of the following conditions apply (i, ii, or iii):
      i. The patient has tried at least one prior systemic therapy for an MSI-H or dMMR solid tumor (for example, gastric, gastroesophageal or esophageal cancers, Ewing sarcoma, osteosarcoma, mesenchymal chondrosarcoma, pancreatic adenocarcinoma, endometrioid carcinomas, penile, adrenal gland, vulvar, cervical, ovarian, fallopian tube, primary peritoneal, testicular); OR
      ii. The patient has unresectable or metastatic gallbladder cancer (including intra- and extra-hepatic cholangiocarcinoma); OR
      iii. The patient has colon or rectal cancer, and ONE of the following apply (a or b):
         i. The patient has tried chemotherapy (e.g., a fluoropyrimadine such as fluorouracil [5-FU], capecitabine; an adjunctive chemotherapy regimen such as FOLFOX [5-FU, leucovorin, and oxaliplatin] or CapeOX [capecitabine and oxaliplatin]); OR
         ii. The patient has metastatic disease and is not a candidate for intensive therapy,[15-16] according to the prescribing physician; AND
   ~~B)~~ Keytruda is prescribed by or in consultation with an oncologist

   Dosing. Approve the following dosing regimens:
   A. 200 mg as an intravenous infusion given once every 3 weeks; OR
   B. 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion given once every 3 weeks.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

9. **Non-Small Cell Lung Cancer.** Approve for 6 months if the patient meets ALL of the following (A, B, and C):
   A. Keytruda is prescribed by or in consultation with an oncologist; AND
   B. The patient meets ONE of the following (i, ii, or iii):
      i. The patient has advanced or metastatic disease and a tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 50%; OR
      ii. The patient's tumor proportion score (TPS) for PD-L1 as determined by an approved test is ≥ 1% AND systemic chemotherapy has been tried (e.g., cisplatin, carboplatin, Alimta [pemetrexed for intravenous injection], gemcitabine, paclitaxel); OR
      iii. Keytruda will be used in combination with chemotherapy (e.g., Alimta [pemetrexed] and carboplatin or cisplatin, paclitaxel, albumin-bound paclitaxel); AND
   C. If non-squamous cell carcinoma (that is, adenocarcinoma, large cell, or NSCLC not otherwise specified) the patient must also meet ONE of the following conditions (i or ii):
      i. The patient's tumor is positive for a targetable mutation (i.e., sensitizing epidermal growth factor receptor [*EGFR*] mutation, anaplastic lymphoma kinase [*ALK*] fusions) AND the patient has received targeted drug therapy for the specific mutation; OR
      ii. The tumor is negative or unknown for these targetable mutations (i.e., *EGFR, ALK).*

   Dosing. Approve the following dosing regimens:
   A) 200 mg as an intravenous infusion every 3 weeks; OR,
   B) In brain metastatses, the following regimens may also be approved:
      i. 10 mg/kg every 2 weeks; OR
      ii. 2 mg/kg every 3 weeks.

   Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
   - Treatment may continue until disease progression or unacceptable toxicity.

10. **Primary Mediastinal Large B-Cell Lymphoma (PMBCL).** Approve for 6 months if the patient meets BOTH of the following (A and B):
   A. The patient has relapsed after, or is refractory to, at least two previous regimens (e.g., autologous hematopoietic stem cell transplant [auto-HSCT], EPOCH-R [etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin, Rituxan {rituximab injection}], RCHOP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone], RCEPP [Rituxan, cyclophosphamide, doxorubicin, vincristine, prednisone]); AND
   B. Keytruda is prescribed by or in consultation with an oncologist.

Dosing. Approve the following dosing regimens:
A) 200 mg as an intravenous infusion given once every 3 weeks; OR
B) 2 mg per kg (up to a maximum of 200 mg) as an intravenous infusion given once every 3 weeks.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
- Treatment may continue until disease progression or unacceptable toxicity.

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11. **Urothelial Carcinoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
    A) The patient meets ONE of the following conditions (i, ii, or iii):
        i. The patient has tried at least one platinum- (cisplatin, carboplatin) containing chemotherapy; OR
        ii. According to the prescribing physician, the patient is not eligible for cisplatin-based chemotherapy, AND the tumor expresses PD-L1 (i.e., has a combined positive score [CPS] ≥ 10); OR
        iii. According to the prescribing physician, the patient is not eligible for platinum-based chemotherapy (i.e., with cisplatin and carboplatin) [Note: this is regardless of PD-L1 status]; AND
    B) Keytruda is prescribed by or in consultation with an oncologist.

    Dosing. Approve if the dose is 200 mg as an intravenous infusion given once every 3 weeks.

    Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
    - Treatment may continue until disease progression or unacceptable toxicity.

Other Uses with Supportive Evidence

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12. **Anal Carcinoma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
    A) The patient has received other chemotherapy (e.g., 5-fluorouracil [5-FU], cisplatin, carboplatin, paclitaxel, FOLFOX [oxaliplatin, leucovorin, and 5-FU]); AND
    B) Keytruda is prescribed by or in consultation with an oncologist.

    Dosing. Approve the following dosing regimens:
    A. 200 mg as an intravenous infusion given once every 3 weeks; OR
    B. 2 mg per kg as an intravenous infusion once every 3 weeks.

Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).

- Treatment may continue until disease progression or unacceptable toxicity.

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13. **Malignant Pleural Mesothelioma.** Approve for 6 months if the patient meets BOTH of the following (A and B):
    A. The patient has tried first-line chemotherapy (e.g., Alimta [pemetrexed intravenous injection] with or without cisplatin or carboplatin, gemcitabine plus cisplatin, vinorelbine); AND
    B. Keytruda is prescribed by or in consultation with an oncologist.

    Dosing. Approve if the dose is one of the following regimens:
    A) 10 mg per kg as an intravenous infusion given once every 2 weeks; OR
    B) 200 mg as an intravenous infusion given once every 3 weeks.

    Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
    - Treatment may continue until disease progression or unacceptable toxicity.

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14. **Small Cell Lung Cancer.** Approve for 6 months if the patient meets BOTH of the following criteria (A and B):
    A. The patient has tried at least one other systemic therapy (e.g., cisplatin, carboplatin, etoposide) within the past 6 months; AND
    B. Keytruda is prescribed by or in consultation with an oncologist.

    Dosing. Approve if the 200 mg as an intravenous infusion given once every 3 weeks.

    Duration of Therapy. Extended approvals are allowed if the patient continues to meet the criteria and dosing (see above).
    - Treatment may continue until disease progression or unacceptable toxicity.

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15. **Other Cancer-Related Indications.** Forward to the Medical Director for review on a case-by-case basis. Other indications supported in the *NCCN Compendium* include mycosis fungoides/Sezary syndrome (category 2A); T-cell lymphoproliferative disorders (2B); extranodal NK/T-cell lymphoma, nasal type (category 2A), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) [2B], gestational trophoblastic neoplasia (2A).

CONDITIONS NOT RECOMMENDED FOR APPROVAL

Keytruda has not been shown to be effective, or there are limited or preliminary data or potential safety concerns that are not supportive of general approval for the following conditions. (Note: This is not an exhaustive list of Conditions Not Recommended for Approval).

1. Coverage is not recommended for circumstances not listed in the Recommended Authorization Criteria. Criteria will be updated as new published data are available.

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Prior approval is required for HCPCS J9271

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Drug Policy

HCPCS Code(s):	
J9271	Injection, pembrolizumab, 1 mg