### Keytruda

#### Description

**Keytruda (pembrolizumab)**

**Background**

Keytruda is a monoclonal antibody for the treatment of patients with advanced or unresectable melanoma, metastatic non-small cell lung cancer (NSCLC), metastatic nonsquamous non-small cell lung cancer (NSCLC), recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), and refractory classical Hodgkin lymphoma (cHL), recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, and microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatments. Keytruda blocks a cellular pathway known as PD-1, human programmed death receptor-1, which restricts the body’s immune system from attacking cancer cells (1-3).

**Regulatory Status**

FDA-approved indication: Keytruda is a human programmed death receptor-1 (PD-1)-blocking antibody indicated for the treatment of: (3)

1. Patients with unresectable or metastatic melanoma
2. Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have high PD-L1 expression [(Tumor Proportion Score (TPS) ≥50%)] as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and no prior systemic chemotherapy treatment for metastatic NSCLC
3. Patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test and who have 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
4. In combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC
5. Patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
6. Adult and pediatric patients with refractory classical Hodgkin lymphoma (cHL), or who have relapsed after 3 or more prior lines of therapy
7. Patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-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
8. Adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options, or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
9. Patients with recurrent locally advanced or metastatic gastric or gastroesophageal junction 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 prior lines of therapy including fluoropyrimidine- and platinum-containing chemotherapy and if appropriate, HER2/neu-targeted therapy

Limitations of Use:
The safety and effectiveness of Keytruda in pediatric patients with MSI-H central nervous system cancers have not been established (3).

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials (3).

Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Patients should be monitored for signs and symptoms of pneumonitis, colitis, hypophysitis, thyroid disorders, and changes in liver and renal function. Keytruda may cause fetal harm when administered to a pregnant woman. Female patients of reproductive potential should be advised of the potential hazard to a fetus (3).

Safety and effectiveness of Keytruda have been established in pediatric patients (3).
**Policy**

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Keytruda may be considered **medically necessary** in patients with unresectable or metastatic melanoma, for metastatic non-small cell lung cancer (NSCLC), for metastatic nonsquamous non-small cell lung cancer (NSCLC), for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), patients with refractory classical Hodgkin lymphoma (cHL), advanced or metastatic urothelial carcinoma, microsatellite instability-high (MSI-H) or a mismatch repair deficient (dMMR) solid tumors, or recurrent locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma; and if the conditions indicated below are met.

Keytruda is considered **investigational** in patients with all other indications.

**Prior-Approval Requirements**

**Diagnoses**

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma

2. Metastatic non-small cell lung cancer (NSCLC) with **ONE** of the following:
   a. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 50% determined by a FDA-approved test
      i. Negative for EGFR or ALK tumor expression
   b. PD-L1 tumor expression with Tumor Proportion Score (TPS) ≥ 1% determined by a FDA-approved test with **ONE** of the following:
      i. Negative for EGFR or ALK tumor expression
         1) Disease progression on or after platinum-containing chemotherapy
      ii. Positive EGFR or ALK tumor expression
         2) Disease progression after targeted FDA-approved therapy
3. Metastatic nonsquamous non-small cell lung cancer (NSCLC)
   a. Used in combination with pemetrexed and carboplatin

4. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
   a. Disease progression on or after platinum-containing chemotherapy

5. Refractory classical Hodgkin lymphoma (cHL)
   a. Patient has relapsed after 3 or more prior lines of therapy

6. Advanced or metastatic urothelial carcinoma with ONE of the following:
   a. Patient is NOT eligible for cisplatin-containing chemotherapy
   b. Disease progression during or following platinum-containing chemotherapy or
      within 12 months of neoadjuvant or adjuvant treatment with platinum-
      containing chemotherapy

7. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers
   with ONE of the following:
   a. Solid tumors that have progressed following prior treatment and who have no
      satisfactory alternative treatment options
      i. NOT for use in pediatric patients with MSI-H central nervous system
         cancers
   b. Colorectal cancer that has progressed following treatment with
      fluoropyrimidine, oxaliplatin, and irinotecan

   AND the following for MSI-H or dMMR cancers:
   a. Diagnosis has to be confirmed by PCR-based assay genetic testing

8. Recurrent locally advanced or metastatic gastric or gastroesophageal junction
   adenocarcinoma
   a. PD-L1 tumor expression with combined positive score (CPS) ≥ 1 as
determined by an FDA-approved test
   b. Disease progression on or after two or more prior lines of therapy including
      fluoropyrimidine- and platinum-containing chemotherapy and if appropriate,
      HER2/neu-targeted therapy

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Prior – Approval Renewal Requirements

Diagnoses
Patient must have ONE of the following:
1. Unresectable or metastatic melanoma
2. Metastatic non-small cell lung cancer (NSCLC)
3. Metastatic nonsquamous non-small cell lung cancer (NSCLC)
4. Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC)
5. Refractory classical Hodgkin lymphoma (cHL)
6. Advanced or metastatic urothelial carcinoma
7. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers
   a. NOT for use in pediatric patients with MSI-H central nervous system cancers
8. Recurrent locally advanced or metastatic gastric or gastroesophageal junction
   adenocarcinoma

AND the following:
   a. Prescriber agrees to discontinue treatment for any immune mediated adverse
      reaction (encephalitis, nephritis, rash, decreased renal function and
      endocrinopathies) or disease progression

Policy Guidelines

Pre - PA Allowance
None

Prior - Approval Limits

Duration 6 months

Prior – Approval Renewal Limits

Duration 12 months

Rationale

Summary
Keytruda is a monoclonal antibody indicated for the treatment of patients with advanced or
unresectable melanoma, metastatic non-small cell lung cancer (NSCLC), metastatic
nonsquamous non-small cell lung cancer (NSCLC), recurrent or metastatic head and neck
squamous cell carcinoma (HNSCC), refractory classical Hodgkin lymphoma (cHL) who are no
longer responding to other drugs, locally advanced or metastatic urothelial carcinoma, recurrent
locally advanced or metastatic gastric or gastroesophageal junction adenocarcinoma, and microsatellite instability-high or mismatch repair deficient solid tumors that have progressed following prior treatments. Clinically significant immune-mediated adverse reactions may occur with Keytruda therapy including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. Based on the severity of the adverse reaction, Keytruda should be withheld or discontinued and corticosteroids administered. Keytruda may cause fetal harm when administered to a pregnant woman. Safety and effectiveness of Keytruda have been established in pediatric patients (1-3).

Prior authorization is required to ensure the safe, clinically appropriate and cost-effective use of Keytruda while maintaining optimal therapeutic outcomes.

References


Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>September 2014</td>
<td>New Policy</td>
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<tr>
<td>December 2014</td>
<td>Annual editorial review and reference update</td>
</tr>
<tr>
<td>June 2015</td>
<td>Annual editorial review</td>
</tr>
<tr>
<td>October 2015</td>
<td>Addition of Metastatic non-small cell lung cancer (NSCLC) if the patient has PD-L1 tumor expression determined by a FDA-approved test and has disease progression on or after platinum-containing chemotherapy; or the patient has EGFR or ALK tumor expression and has disease progression after FDA-approved therapy</td>
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<tr>
<td>December 2015</td>
<td>Annual review Removal of disease progression following Yervoy (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor and no concurrent therapy with other agents for the treatment of unresectable or metastatic</td>
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Section: Prescription Drugs  Effective Date: January 1, 2018
Subsection: Antineoplastic Agents  Original Policy Date: September 26, 2014
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Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 8, 2017 and is effective on January 1, 2018.