I. Policy:
Keytruda (pembrolizumab)

II. Purpose/Objective:
To provide a policy of coverage regarding Keytruda (pembrolizumab)

III. Responsibility:
A. Medical Directors
B. Medical Management
C. Pharmacy Department

IV. Required Definitions
1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions
Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
b. provided for the diagnosis and the direct care and treatment of the Member's condition, illness disease or injury;
c. in accordance with current standards good medical treatment practiced by the general medical community;
d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient

Medical Business Segment
Medical Necessity shall mean a service or benefit that is compensable under the Medical Assistance Program and if it meets any one of the following standards:

(i) the service or benefit will, or is reasonably expected to, prevent the onset of an illness, condition or disability.

(ii) the service or benefit will, or is reasonably expected to, reduce or ameliorate the physical, mental or development effects of an illness, condition, injury or disability.

(iii) the service or benefit will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for members of the same age
DESCRIPTION:
Keytruda (pembrolizumab) binds to the programmed death receptor-1 (PD-1) ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production.

CRITERIA FOR USE: Requires Prior Authorization by Medical Director or Designee

GRANDFATHER PROVISION – Members already established on therapy are eligible for approval as long as there is medical record documentation that the safety and effectiveness of use for the prescribed indication is supported by Food and Drug Administration (FDA) approval or adequate medical and scientific evidence in the medical literature.

Keytruda (pembrolizumab) will be considered medically necessary when all of the following criteria are met:

1. Melanoma
   - Prescription written by a hematologist/oncologist AND
   - Medical record documentation that patient is ≥ 18 years of age AND
   - Medical record documentation of a diagnosis of unresectable or metastatic melanoma AND
     - Medical record documentation of one of the following:
       - Unresectable or metastatic melanoma:
         - A diagnosis of unresectable or metastatic melanoma AND
         - Keytruda is not being used in combination with any other agents for the treatment of unresectable or metastatic melanoma.
       - OR
         - Adjuvant treatment of completely resected metastatic melanoma
           - A diagnosis of metastatic melanoma with lymph node involvement, which has been completely resected AND
           - Keytruda is being used in the adjuvant setting (following lymph node resection) AND
           - Keytruda is being used as a single agent.

2. Metastatic Non-Small Cell Lung Cancer (NSCLS)
   - Prescription written by a hematologist/oncologist AND
   - Medical record documentation that patient is ≥ 18 years of age AND
   - Medical record documentation of a diagnosis of metastatic NSCLC meeting one of the following situations:
     - Medical record documentation of stage III NSCLC, metastatic NSCLC, OR that the member is not a candidate for surgical resection or definitive chemoradiation AND
     - Medical record documentation that Keytruda is being used as first-line treatment AND
     - Medical record documentation that Keytruda is being given as monotherapy AND
     - Medical record documentation that tumors express PD-L1 (TPS) ≥1% as determined by an FDA-approved test AND
     - Medical record documentation that tumors do not have EGFR or ALK genomic tumor aberrations
     - OR
     - Medical record documentation that Keytruda is being given as monotherapy AND
     - Medical record documentation that tumors express PD-L1 (TPS) ≥1% as determined by an FDA-approved test AND
     - Medical record documentation of disease progression on or after platinum-containing chemotherapy AND
     - For patients with EGFR or ALK genomic tumor aberrations: medical record documentation of disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
     - OR
     - Medical record documentation of metastatic nonsquamous NSCLC AND
     - Medical record documentation that Keytruda will be given in combination with pemetrexed AND either carboplatin or cisplatin AND
     - Medical record documentation that tumors do not have EGFR or ALK genomic tumor aberrations
     - OR
     - Medical record documentation that Keytruda will be given in combination with carboplatin AND either paclitaxel or nab-paclitaxel AND
     - Medical record documentation that Keytruda, carboplatin, and paclitaxel (or nab-paclitaxel) are being used as first-line treatment.
3. **Head and Neck Squamous Cell Carcinoma**
   - Prescription written by a hematologist/oncologist **AND**
   - Medical record documentation that patient is ≥ 18 years of age **AND**
   - Medical record documentation of one of the following:
     - A diagnosis of Head and Neck Squamous Cell Carcinoma that is recurrent or metastatic **AND**
     - Disease progression on or after platinum-containing chemotherapy **AND**
     - Keytruda is being used as a single agent.
   - OR
     - A diagnosis of metastatic or unresectable, recurrent Head and Neck Squamous Cell Carcinoma **AND**
     - Keytruda is being used as a first-line treatment **AND**
     - Keytruda is being used as a single agent **AND**
     - Tumors express PD-L1 [Combined Positive Score (CPS) ≥ 1] as determined by an FDA-approved test
   OR
     - A diagnosis of metastatic or unresectable, recurrent Head and Neck Squamous Cell Carcinoma **AND**
     - Keytruda is being used as a first-line treatment **AND**
     - Keytruda is being administered in combination with platinum chemotherapy and fluorouracil (FU)

4. **Classical Hodgkin Lymphoma**
   - Prescription written by a hematologist/oncologist **AND**
   - Medical record documentation of Classical Hodgkin Lymphoma **AND**
   - One of the following:
     - a. Medical record documentation of a diagnosis of refractory Classical Hodgkin Lymphoma **OR**
     - b. Medical record documentation of relapse following three (3) or more prior lines of therapy

5. **Microsatellite Instability-High Cancer**
   - Prescription written by a hematologist/oncologist **AND**
   - Medical record documentation of unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors OR colorectal cancer **AND**
   - For solid tumors:
     - Medical record documentation of progression following prior treatment(s) **AND**
     - Medical record documentation of no satisfactory alternative treatment options
   - For colorectal cancer:
     - Medical record documentation of progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan

6. **Urothelial Carcinoma**
   - Prescription written by a hematologist/oncologist **AND**
   - Medical record documentation that patient is ≥ 18 years of age **AND**
   - Medical record documentation of locally advanced or metastatic urothelial carcinoma **AND**
   - Medical record documentation of one of the following:
     - Disease progression during or following platinum-containing chemotherapy **OR**
     - Disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy **OR**
     - Patient is not eligible cisplatin-containing chemotherapy* **AND**
     - Tumors express PD-L1 (combined positive score [CPS] greater than or equal to 10) as determined by an FDA-approved test **OR**
     - Patient is not eligible for any platinum-containing chemotherapy (regardless of PD-L1 status)

*Note: In clinical trials, patients who were not considered cisplatin-eligible had the following characteristics: baseline creatinine clearance of <60 mL/min, ECOG performance status of 2, ECOG 2 and baseline creatinine clearance of <60 mL/min, other reasons (Class III heart failure, Grade 2 or greater peripheral neuropathy, and Grade 2 or greater hearing loss).

7. **Gastric Cancer**
   - Prescription written by a hematologist/oncologist **AND**
• Medical record documentation of a diagnosis of recurrent locally advanced or metastatic gastric or
gastroesophageal junction adenocarcinoma **AND**
• Medical record documentation that tumors express PD-L1 (combined positive score [CPS] greater than or equal
to 1) as determined by an FDA-approved test **AND**
• Medical record documentation of disease progression on or after two or more prior lines of therapy (including
fluoropyrimidine- and platinum-containing chemotherapy)**AND**
• If patient has HER2-positive disease, medical record documentation of disease progression on or after
HER2/neu-targeted therapy (including but not limited to trastuzumab (Herceptin))**

*Note to reviewer: Current recommendations intend Keytruda to be used as third-line treatment (i.e. patient is to
have 2 prior lines of therapy, one of which must include HER2/neu-targeted therapy if the patient has HER-2
positive disease)

8. Cervical Cancer
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation of recurrent or metastatic cervical cancer **AND**
• Medical record documentation that tumors express PD-L1 (CPS≥1) **AND**
• Medical record documentation of disease progression after receiving at least one prior line of therapy

9. Primary Mediastinal Large B-cell Lymphoma (PMBCL)
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation of refractory primary mediastinal large B-cell lymphoma (PMBCL) **OR**
• Medical record documentation of relapse following two (2) prior lines of therapy

10. Hepatocellular Carcinoma (HCC)
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation that patient is ≥ 18 years of age **AND**
• Medical record documentation of a diagnosis of hepatocellular carcinoma **AND**
• Medical record documentation of a therapeutic failure on or intolerance to sorafenib (Nexavar)

11. Merkel Cell Carcinoma (MCC)
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation of a diagnosis of Merkel Cell Carcinoma **AND**
• Medical record documentation of metastatic and/or recurrent disease

12. Renal Cell Carcinoma (RCC)
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation that patient is ≥ 18 years of age **AND**
• Medical record documentation of a diagnosis of advanced renal cell carcinoma **AND**
• Medical record documentation that Keytruda is being used in combination with axitinib (Inlyta) **AND**
• Medical record documentation that Keytruda and axitinib (Inlyta) are being used as first-line treatment for
advanced disease

*Note: In clinical trials, advanced disease included newly diagnosed or recurrent Stage IV renal cell carcinoma.

13. Small Cell Lung Cancer (SCLC)
• Prescription written by a hematologist/oncologist **AND**
• Medical record documentation that patient is ≥ 18 years of age **AND**
• Medical record documentation of a diagnosis of metastatic small cell lung cancer (SCLC) **AND**
• Medical record documentation of disease progression on or after two lines of therapy, one of which must be
platinum-based chemotherapy
14. Esophageal Cancer
- Prescription written by a hematologist/oncologist **AND**
- Medical record documentation that patient is ≥ 18 years of age **AND**
- Medical record documentation of a diagnosis of locally advanced or metastatic squamous cell carcinoma of the esophagus **AND**
- Medical record documentation that tumors express PD-L1 (CPS ≥10) as determined by an FDA-approved test **AND**
- Medical record documentation of disease progression after one or more prior lines of systemic therapy for advanced disease.

15. Endometrial Carcinoma
- Prescription written by a hematologist/oncologist **AND**
- Medical record documentation of a diagnosis of advanced endometrial carcinoma **AND**
- Medical record documentation of disease progression following at least one prior systemic therapy **AND**
- Medical record documentation that patient is not a candidate for curative surgery or radiation **AND**
- Medical record documentation that tumors are not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) **AND**
- Medical record documentation that Keytruda will be given in combination with lenvatinib (Lenvima)

**LIMITATIONS**: The treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials.

**AUTHORIZATION DURATION**: Initial approval will be for **6 months** or less if the reviewing provider feels it is medically appropriate. Subsequent approvals will be for an additional **12 months** or less if the reviewing provider feels it is medically appropriate and will require medical record documentation of continued disease improvement or lack of disease progression. The medication will no longer be covered if patient experiences toxicity or worsening of disease.

**LINE OF BUSINESS**: Eligibility and contract specific benefit limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy.

This policy will be revised as necessary and reviewed no less than annually.

**Devised**: 11/18/14

**Revised**: 9/20/16 (new indication), 11/17/15 (NSCLC indication), 1/17/17 (NSCLC update), 5/16/17 (CHL indication), 7/18/17 (added indications, MSI-H, urothelial, updated NSCLC), 11/21/17 (gastric cancer), 7/17/18 (cervical cancer), 9/18/18 (PMBCL, urothelial, NSCLC), 1/15/19 (NSCLC, HCC, MCC), 5/21/19 (Melanoma, NSCLC, RCC), 7/16/19 (SCLC, head and neck), 9/17/19 (esophageal), 11/19/19 (endometrial)

**Reviewed**: 3/24/15 (removed failure on other agents)