

Clinical Policy: Pembrolizumab (Keytruda)

Reference Number: CP.PHAR.322

Effective Date: 03/17

Last Review Date: 03/17

[Coding Implications](#)
[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

Description

The intent of the criteria is to ensure that patients follow selection elements established by Centene® clinical policy for pembrolizumab for injection (Keytruda®).

Policy/Criteria

It is the policy of health plans affiliated with Centene Corporation® that Keytruda is **medically necessary** when the following criteria are met:

I. Initial Approval Criteria

A. Melanoma (must meet all):

1. Diagnosis of melanoma;
2. Disease is unresectable or metastatic;
3. Prescribed dose does not exceed 2 mg/kg administered every 3 weeks.

Approval duration: 3 months

B. Non-Small Cell Lung Cancer (must meet all):

1. Diagnosis of non-small cell lung cancer (NSCLC);
2. Disease is recurrent or metastatic;
3. Meets a or b:
 - a. FDA approved use (i or ii):
 - i. First-line therapy (a and b):
 - a) Tumor PD-L1 expression $\geq 50\%$ (Tumor Proportion Score [TPS]);
 - b) EGFR and ALK mutation status negative or unknown;
 - ii. Subsequent therapy (a and b):
 - a) Tumor PD-L1 expression $\geq 1\%$ (TPS);
 - b) Disease has progressed on or after (1, 2 or 3):
 - 1) Platinum containing chemotherapy if EGFR and ALK mutation status negative or unknown;
 - 2) FDA-approved therapy if EGFR mutation status is positive (e.g., erlotinib, afatinib, gefitinib, osimertinib);
 - 3) FDA-approved therapy if ALK mutation status is positive (e.g., crizotinib, ceritinib, alectinib);
 - b. Off-label NCCN recommended use (i or ii):
 - i. First-line therapy (a and b):
 - a) Tumor PD-L1 expression $\geq 50\%$ (TPS);
 - b) ROS1 mutation status negative or unknown;
 - ii. Subsequent therapy and (a or b):
 - a) Tumor PD-L1 expression $\geq 50\%$ (TPS) (1) :

- 1) ROS1 mutation status positive and member has received crizotinib therapy;
- b) Tumor PD-L1 expression $\geq 1\%$ (TPS) and systemic immune checkpoint inhibitors have not yet been given (e.g., nivolumab, pembrolizumab, atezolizumab) (1 or 2):
 - 1) Following progression on a first-line cytotoxic regimen (first-line regimens not limited to platinum-containing chemotherapy);
 - 2) For further progression on other systemic therapy.

Approval duration: 3 months

C. Head and Neck Squamous Cell Carcinoma (must meet all):

1. Diagnosis of head and neck squamous cell carcinoma (HNSCC) (see Appendix B for subtypes by location);
2. Disease has progressed on or after platinum-containing chemotherapy;
3. Meets a or b:
 - a. FDA approved use:
 - i. Disease is recurrent or metastatic;
 - b. Off-label NCCN recommended use:
 - i. Prescribed as a single agent (a, b or c):
 - a) Disease or other factors preclude surgery;
 - b) Very advanced (T4b*) nonmetastatic disease;
 - c) Unresectable disease with the following characteristics (1 or 2):
 - 1) Nodal disease with no metastases;
 - 2) Second primary tumor and member has received prior radiation therapy.

**American Joint Committee on Cancer () TNM staging classification (7th ed., 2010) as reported in NCCN Head and Neck Cancers: T (primary tumor characteristics); N (regional lymph nodes); M (metastatic disease).*

Approval duration: 3 months

D. Other diagnoses/indications: Refer to CP.PHAR.57 - Global Biopharm Policy.

1. The following NCCN recommended uses for Keytruda, meeting NCCN categories 1, 2a, or 2b, are approved per the CP.PHAR.57 Global Biopharm Policy:
 - a. Colon cancer;
 - b. Rectal cancer;
 - c. Classical Hodgkin lymphoma;
 - d. Merkel cell carcinoma (non-melanoma skin cancer subtype).

II. Continued Approval

A. All Indications (must meet all):

1. Currently receiving medication via Centene benefit or member has previously met all initial approval criteria;
2. Member has none of the following reasons to discontinue:

- a. Disease progression or unacceptable toxicity;
- b. Immune mediated hepatitis:
 - i. Increase of total bilirubin to > 3 times upper limit of normal (ULN);
 - ii. Increase of AST/ALT to > 5 times ULN;
 - iii. If liver metastasis and AST/ALT > 3 to 5 times ULN at initiation of therapy, increase of AST/ALT to \geq 50% lasting for \geq 1 week;
- c. Grade 2 through Grade 4 adverse reactions:^{*†}
 - i. Grade 2 (moderate) or higher:
 - a) Recurrent pneumonitis;
 - b) Any adverse reaction that does not recover to Grade 1 (mild) within 12 weeks after the last dose of Keytruda;
 - ii. Grade 3 (severe) or higher:
 - a) Nephritis;
 - b) Infusion reaction;
 - c) First occurrence or recurrence of pneumonitis;
 - d) Any adverse reaction that recurs;
 - iii. Grade 4 (life-threatening):
 - a) Any adverse reaction.

^{*}Grading is based on the Common Terminology Criteria for Adverse Events.

[†]Graded adverse reactions exclude endocrinopathies controlled with hormone replacement therapy.

Approval duration: 6 months

B. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy; or
2. Refer to CP.PHAR.57 - Global Biopharm Policy.

Background

Description/Mechanism of Action:

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Formulations:

Keytruda for injection is supplied as follows:

- Lyophilized powder:
 - 50 mg single-use vial; concentration of 25 mg/mL after reconstitution
- Solution:
 - 100 mg/4 mL (25 mg/mL), single-use vial

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FDA Approved Indications:

Keytruda is a programmed death receptor-1 (PD-1)-blocking antibody/intravenous formulation indicated for:

- Melanoma
 - Treatment of patients with unresectable or metastatic melanoma.
- Non-small cell lung cancer
 - First-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have
 - High PD-L1 expression [Tumor Proportion Score (TPS) $\geq 50\%$] as determined by an FDA-approved test,
 - With no EGFR or ALK genomic tumor aberrations.
 - Treatment of patients with metastatic NSCLC whose tumors express
 - PD-L1 (TPS $\geq 1\%$) as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy.
 - Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.
- Head and neck cancer
 - Treatment of patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.
 - 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.

Appendices

Appendix A: Abbreviation Key

ALK: Anaplastic lymphoma receptor
 EGFR: Epidermal growth factor receptor
 HNSCC: Head and neck squamous cell carcinoma
 NSCLC: Non-small cell lung cancer

PD-1: Programmed cell death protein 1
 PD-L1/2: Programmed death ligand 1/2
 ROS1: ROS proto-oncogene 1, receptor tyrosine kinase
 TPS: Tumor proportion score

Appendix B: Head and Neck Squamous Cell Cancers by Location*⁵

- Paranasal sinuses (ethmoid, maxillary)
- Larynx (glottis, supraglottis)
- Pharynx (nasopharynx, oropharynx, hypopharynx)
- Lip and oral cavity
- Major salivary glands (parotid, submandibular, sublingual)
- Occult primary

*Squamous cell carcinoma, or a variant, is the histologic type in more than 90% of head and neck cancers.

Coding Implications

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Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9271	Injection, Pembrolizumab, 1mg

Reviews, Revisions, and Approvals	Date	Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. Non-small cell lung cancer: NCCN off-label recommendations added; “recurrent or” added to “metastatic disease” and “or unknown” added to “negative mutation status” to consolidate criteria of those FDA/NCCN uses that differed by the referenced terms. Head and neck cancers: NCCN off-label recommended uses added; subtypes by location outlined at Appendix B.	01/17	03/17

References

1. Keytruda prescribing information. Whitehouse Station, NJ: Merck and Co.; October 2016. Available at http://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf. Accessed January 23, 2017.
2. Pembrolizumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at NCCN.org. Accessed January 23, 2017.
3. Melanoma (Version 1.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 23, 2017.
4. Non-small cell lung cancer (Version 4.2017). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 23, 2017.
5. Head and neck cancers (Version 2.2016). In: National Comprehensive Cancer Network Guidelines. Available at NCCN.org. Accessed January 23, 2017.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a

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contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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Note: For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at <http://www.cms.gov> for additional information.

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