Nivolumab (Opdivo®)

Prior Authorization Drug Coverage Policy

Effective Date: 1/1/2021
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Lines of Business: Commercial
Policy type: Prior Authorization

This Drug Coverage Policy provides parameters for the coverage of nivolumab. Consideration of medically necessary indications are based upon U.S. Food and Drug Administration (FDA) indications, recommended uses within the Centers of Medicare & Medicaid Services (CMS) five recognized compendia, including the National Comprehensive Cancer Network (NCCN) Drugs & Biologics Compendium (Category 1 or 2A recommendations), and peer-reviewed scientific literature eligible for coverage according to the CMS, Medicare Benefit Policy Manual, Chapter 15, section 50.4.5 titled, "Off-Label Use of Anti-Cancer Drugs and Biologics." This policy evaluates whether the drug therapy is proven to be effective based on published evidence-based medicine.

Drug Description[1]

- Binding of the programmed death ligand (PD-L), PD-L1 and PD-L2, to the programmed death receptor-1 (PD-1) 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. Nivolumab is a human immunoglobulin G4 (IgG4) 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.

- Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma and advanced RCC. In murine syngeneic tumor models, dual blockade of PD-1 and CTLA-4 resulted in increased anti-tumor activity.

FDA Indications[1]

Nivolumab is FDA indicated for the following:

- **Melanoma**
  - Indicated for the treatment of patients with unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
  - Indicated for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- **Non-Small Cell Lung Cancer**
  - Indicated for the treatment of patients with metastatic NSCLC expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with ipilimumab.
  - Indicated for the treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy.
  - Indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
- **Malignant Pleural Mesothelioma**
  - Indicated for the treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with ipilimumab.
- **Renal Cell Carcinoma**
  - Indicated for the treatment of patients with intermediate or poor risk advanced renal cell carcinoma, as a first-line treatment in combination with ipilimumab.
  - Indicated for the treatment of patients with advanced renal cell carcinoma, as a first-line treatment in combination with cabozantinib.
  - Indicated for the treatment of patients with advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- **Classical Hodgkin Lymphoma (cHL)**
  - Indicated for the treatment of adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after:
    - autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin, ***OR***
    - 3 or more lines of systemic therapy that includes autologous HSCT.
- **Squamous Cell Carcinoma of the Head and Neck**
  - Indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.
- **Urothelial Carcinoma**
  - Indicated for the adjuvant treatment of patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

    - Indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who:
        - have disease progression during or following platinum-containing chemotherapy
        - have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.
- **Colorectal Cancer**
    - Administered as a single agent or in combination with ipilimumab, is indicated for the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.
- **Hepatocellular Carcinoma (HCC)**
    - Indicated for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib in combination with ipilimumab.
- **Esophageal Squamous Cell Carcinoma (ESCC)**
    - Indicated for patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy (CRT).
    - Indicated for patients with unresectable advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC) after prior fluoropyrimidine- and platinum-based chemotherapy.
- **Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma**
    - Indicated for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy.

NCCN Compendium Supported Indications[2]

- Melanoma: Uveal
- Anal Cancer
- Gestational Trophoblastic Neoplasia
- Merkel Cell Carcinoma
- Small Bowel Adenocarcinoma
- Small-Cell Lung Cancer
- T-Cell Lymphomas
- Uterine Neoplasms
- Vulvar Cancer

Coverage Determinations[1,2]

Nivolumab will require prior authorization. This agent may be considered medically necessary for the following oncology indications if all criteria below are met:

Melanoma: Cutaneous

- Member must have a diagnosis of melanoma
- Member must have resected stage III melanoma with no evidence of disease following resection **AND**
- Nivolumab must be used as a single agent **OR**
- Member must have a diagnosis of unresectable or metastatic melanoma in the front-line or subsequent setting **OR**
- Nivolumab will be utilized as a single agent or in combination with ipilimumab

Melanoma: Uveal

- Member must have a diagnosis of distant metastatic disease
- Nivolumab will be utilized as a single agent or in combination with ipilimumab

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks in patients with unresectable or metastatic melanoma **OR**
- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks up to 12 months in adjuvant melanoma without disease recurrence or unacceptable toxicity **OR**
- (in combination with ipilimumab) Administer nivolumab as 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks

Non-small cell lung cancer

- Member must have a diagnosis of squamous or non-squamous NSCLC **AND**
- Member must have newly diagnosed stage IV NSCLC **AND**
    - Disease will express PD-L1 $\geq$ 1% **AND**
    - Treatment is used in the first-line setting **AND**
    - Nivolumab will be utilized in combination with ipilimumab
- Member must have newly diagnosed stage IV NSCLC **AND**
    - Treatment is used in the first-line setting **AND**
    - Nivolumab will be utilized in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy
- Member must have a diagnosis of stage IV NSCLC **AND**
    - Member must have failed one prior therapy for advanced NSCLC including platinum-based chemotherapy or EGFR-targeted agent or ALK-targeted agent if EGFR or ALK mutation positive **AND**
    - Nivolumab will be utilized as a single agent

Recommended dosage

- Administer nivolumab as 3 mg/kg every 2 weeks with ipilimumab 1 mg/kg every 6 weeks **OR**
- Administer nivolumab as 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-doublet chemotherapy **OR**
- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Malignant Pleural Mesothelioma

- Member must have a diagnosis of:
    - unresectable clinical stage I-IIIA disease and epithelioid or biphasic histology **OR**
    - clinical stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors
        - Nivolumab will be used first-line in combination with ipilimumab **OR**
        - Preferred subsequent systemic therapy, if not administered first-line
            - as a single agent **OR**
            - in combination with ipilimumab

Recommended dosage

- First-Line therapy: Administer nivolumab as 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks **OR**
- Subsequent therapy: Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks with or without ipilimumab 1 mg/kg every 6 weeks

Renal cell carcinoma (RCC)

- Member must have a diagnosis of advanced or metastatic RCC **AND**
    - Nivolumab will be used in combination with cabozantinib in clear cell histology as:
        - Preferred first-line therapy for favorable risk **OR**
        - Preferred first-line therapy for poor/intermediate risk **OR**
        - Subsequent therapy
    - Nivolumab will be used in combination with ipilimumab for 4 cycles followed by single agent nivolumab in clear cell histology as:
        - First-line therapy for favorable risk **OR**
        - Preferred first-line therapy for poor/intermediate risk **OR**
        - Subsequent therapy
    - Nivolumab will be used as a single agent as:
        - preferred subsequent therapy for clear cell histology **OR**
        - systemic therapy for non-clear cell histology

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks ***OR***
- Administer nivolumab as 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks.

Classical Hodgkin Lymphoma (cHL)

- Member must have a diagnosis of Classical Hodgkin Lymphoma **AND**
- The member has relapsed disease **AND**
- Nivolumab will be used as monotherapy **AND**
- Nivolumab will be used second-line or subsequent systemic therapy (if not previously used) for relapsed or refractory disease in combination with brentuximab vedotin **OR**
- Nivolumab will be used in the third line or subsequent setting for:
    - Disease that has relapsed or progressed after autologous hematopoietic stem cell transplant (HSCT) ± brentuximab vedotin **OR**
    - Patient is HSCT ineligible **OR**
    - Post-allogeneic transplant

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks.

Squamous Cell Carcinoma of the Head and Neck (SCCHN)

- Member must have a diagnosis of recurrent or metastatic squamous cell carcinoma of the head and neck **AND**
- Nivolumab will be used as subsequent therapy **AND**
- Nivolumab will be used as a single agent **AND**
- Member has developed progressive or recurrent disease following platinum-based treatment

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Urothelial Carcinoma

- The member has a diagnosis of metastatic or locally advanced urothelial carcinoma **AND**
    - The member has disease progression during or following platinum-containing chemotherapy **OR**
    - The member has disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy **OR**
- The member has undergone a radical resection and are at a high risk of recurrence **AND**
    - Nivolumab will be used as a single agent as adjuvant treatment

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks.

Colorectal Cancer: Microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR)

- Member must have a diagnosis of MSI-H or dMMR colorectal cancer
- Nivolumab will be used as a single agent **OR** in combination with ipilimumab
- One of the following applies:

- The member has disease that has progressed on oxaliplatin, irinotecan, or fluorouracil-based treatment
- The member has unresectable metachronous metastases and has utilized FOLFOX (fluorouracil, oxaliplatin, leucovorin) or CapeOx (capecitabine, oxaliplatin) within the last 12 months

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks ***OR***
  - Administer nivolumab as 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks

Hepatocellular carcinoma

- Member must have a diagnosis of progressive hepatocellular carcinoma **AND**
  - have unresectable disease and are not a transplant candidate **OR**
  - have liver-confined disease, inoperable by performance status, comorbidity or with minimal or uncertain extrahepatic disease **OR**
  - have metastatic disease or extensive liver tumor burden **AND**
- Nivolumab will be used in combination with ipilimumab in the subsequent setting

Recommended dosage

- Administer nivolumab as 1 mg/kg followed by ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks.

Esophageal Cancer

- Nivolumab will be used as adjuvant treatment in patients with completely resected esophageal or gastroesophageal junction cancer with residual pathologic disease, who have received neoadjuvant chemoradiotherapy
  - Nivolumab will be used as a single agent
- Member must have a diagnosis of unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma **AND**
  - Nivolumab will be used as second-line or subsequent therapy after prior fluoropyrimidine- and platinum-based chemotherapy.

Recommended dosage

- Adjuvant Nivolumab:
  - Administer nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks for 16 weeks, then 480 mg every 4 weeks for total treatment duration of 1 year
- Second-line Nivolumab:
  - Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Gastric Cancer, Gastroesophageal Junction Cancer, and Esophageal Adenocarcinoma

- Member must have a diagnosis of advanced or metastatic gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma **AND**
- Nivolumab will be used in combination with fluoropyrimidine- and platinum-containing chemotherapy

Recommended dosage

- Administer nivolumab as 360 mg every 3 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 3 weeks.
- Administer nivolumab 240 mg every 2 weeks with fluoropyrimidine- and platinum-containing chemotherapy every 2 weeks

Merkel Cell Carcinoma

- Member must have a diagnosis of clinical M1 or recurrent disseminated disease with or without surgery and/or radiation therapy
- Nivolumab will be used as a single agent

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Anal Carcinoma

- Member must have a diagnosis of squamous metastatic anal carcinoma
- Nivolumab will be used as subsequent therapy
- Nivolumab will be used as a single agent

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Gestational Trophoblastic Neoplasia

- Useful in certain circumstances as single-agent therapy for:
    - multiagent chemotherapy-resistant high-risk disease **OR**
    - recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor) following treatment with a platinum/etoposide-containing regimen

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Small Bowel Adenocarcinoma

- The member will be using nivolumab as a single agent or in combination with ipilimumab for advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) for **ANY** of the following:
    - Initial therapy if no previous treatment with a checkpoint inhibitor **OR**

- Subsequent therapy if no previous treatment with a checkpoint inhibitor and no prior oxaliplatin exposure in the adjuvant setting or contraindication to oxaliplatin

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks ***OR***
  - Administer nivolumab as 3 mg/kg followed by ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 mg every 4 weeks

Small cell lung cancer

- Member must have a diagnosis of extensive stage or metastatic SCLC **AND**
- Nivolumab will be used as a single agent as subsequent therapy for:
  - Relapse following complete or partial response or stable disease with primary treatment (The use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse)
  - Primary progressive disease

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

T-Cell Lymphoma

- Member has a diagnosis of Extranodal Natural Killer Cell Lymphoma/T-Cell Lymphoma, nasal type **AND**
- Patient has relapsed or refractory disease following additional therapy with an alternate combination chemotherapy regimen (asparaginase-based chemotherapy) not previously used

Recommended dosage

- Administer nivolumab as 40 mg every 2 weeks[4]

Uterine Neoplasms

- Member must have a diagnosis of MSI-H or dMMR Endometrial Cancer
- Nivolumab will be used as a single agent, second-line therapy

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

Vulvar Cancer

- Member has a diagnosis of HPV-related advanced, recurrent, or metastatic disease **AND**
- Nivolumab will be used as second-line therapy

Recommended dosage

- Administer nivolumab as 240 mg every 2 weeks or 480 mg every 4 weeks

All indications:

- Nivolumab will be approved for a up to a 6-month duration or as determined through clinical review.

Coverage Limitations

Treatment with nivolumab is not considered medically necessary for members with the following concomitant conditions:

- The member has experienced disease progression on nivolumab.
- The member has experienced disease progression while on or following another PD-1/PD-L1 directed therapy
- For melanoma, may be considered as re-induction therapy (as a single agent or in combination with ipilimumab) if prior anti-PD-1 checkpoint inhibitor immunotherapy resulted in disease control (complete response, partial response, or stable disease) and no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation
- Indications not supported by NCCN category 2A or higher recommendations may not be considered medically necessary

Contraindications/Warnings/Precautions[1]

- There are no contraindications listed in the US manufacturer's labeling.
- Warnings/precautions:
    - Immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, nephritis and renal dysfunction, skin adverse reactions, encephalitis
    - Infusion-Related Reactions
    - Complications of allogeneic HSCT
    - Embryo-Fetal Toxicity

Billing

- Description: Nivolumab, 1 mg
    - J9299

Disclaimer

Drug Coverage Policies are developed as needed, regularly reviewed, updated at least annually, and are subject to change. Other policies and coverage determination guidelines

may apply. Federal and state regulatory requirements and member specific benefit plan documents, if applicable, must be reviewed prior to this Drug Coverage Policy. This Drug Coverage Policy is for informational purposes only and does not constitute medical advice or dictate how providers should practice medicine. This policy should not be reproduced, stored in a retrieval system, or altered from its original form without written permission from Oncology Analytics, Inc.

References

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