Ipilimumab (Yervoy®)

Prior Authorization Drug Coverage Policy

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Lines of Business: Commercial
Policy type: Prior Authorization

This Drug Coverage Policy provides parameters for the coverage of ipilimumab. 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]

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

FDA Indications[1]

Ipilimumab is FDA indicated for the following:

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older).
- Treatment of adult patients with unresectable or metastatic melanoma, in combination with nivolumab.
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.
- Treatment of patients with intermediate or poor-risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab.
- Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response.

Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

- Treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab. This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.
- Treatment of adult patients with metastatic non-small cell lung cancer 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 nivolumab.
- 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 nivolumab and 2 cycles of platinum-doublet chemotherapy.
- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab.

NCCN Compendium Supported Indications[2]

- Melanoma: Cutaneous
- Melanoma: Uveal
- Kidney Cancer
- Colon Cancer
- Hepatobiliary Cancer- Hepatocellular Carcinoma
- Central Nervous System Cancer- Extensive Brain Metastases
- Central Nervous System Cancer- Limited Brain Metastases
- Malignant Pleural Mesothelioma
- Non-Small Cell Lung Cancer
- Rectal Cancer
- Small Bowel Adenocarcinoma

Coverage Determinations[1,2]

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

Melanoma: Cutaneous

- The member will be using ipilimumab as adjuvant treatment for cutaneous melanoma as a high-dose single agent is useful under certain circumstances (if prior exposure to anti-PD-1 therapy) in **ANY** of the following:
    - Following complete lymph node dissection and/or complete resection of nodal recurrence; **OR**
    - Following complete resection of distant metastatic disease; **OR**

- As first-line therapy in combination with nivolumab for metastatic or unresectable cutaneous melanoma; **OR**
- As second-line or subsequent therapy for metastatic or unresectable cutaneous melanoma after disease progression or maximum clinical benefit from BRAF-targeted therapy in **ANY** of the following:
    - As a single agent if checkpoint inhibitor immunotherapy was not previously used; **OR**
    - In combination with nivolumab if checkpoint inhibitor immunotherapy was not previously used or for individuals who progress on single agent checkpoint inhibitor immunotherapy; **OR**
    - In combination with intralesional injection of talimogene laherparepvec; **or**
    - As re-induction therapy as a single agent or in combination with nivolumab if prior checkpoint inhibitor immunotherapy resulted in disease control and no residual toxicity, and disease progression/relapse occurred greater than three months after treatment discontinuation

Melanoma: Uveal

- The member has a diagnosis of uveal melanoma with distant metastatic disease.
    - The member will receive ipilimumab as single-agent therapy **OR**
    - The member will receive ipilimumab in combination with nivolumab

Recommended dosage:

- Unresectable or metastatic melanoma:
    - Ipilimumab 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses.
- Adjuvant melanoma:
    - Ipilimumab 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.
    - Ipilimumab 3mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 3 mg/kg every 12 weeks for up to 4 additional doses (maintenance). (Off-label dosing)

Renal Cell Carcinoma

- The member will be using Ipilimumab in combination with nivolumab for up to 4 cycles followed by single-agent nivolumab for relapsed or stage IV disease **AND**:
    - As first-line therapy for clear cell histology and poor/intermediate risk

Recommended dosage: Ipilimumab 1 mg/kg administered intravenously over 30 minutes on the same day every 3 weeks for 4 doses given in combination with nivolumab, then nivolumab monotherapy.

Colorectal Cancer

- The member will be using ipilimumab as combination therapy with nivolumab for **ANY** of the following (dMMR/MSI-H only):
    - as neoadjuvant therapy for resectable synchronous liver and/or lung metastases
    - for unresectable synchronous liver and or lung metastases only
    - for unresectable metachronous metastases and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months
    - as primary treatment for locally unresectable or medically inoperable disease
    - for unresectable synchronous liver and/or lung metastases that remain unresectable after primary systemic therapy
    - as primary treatment for synchronous abdominal/peritoneal metastases that are nonobstructing, or following local therapy for patients with existing or imminent obstruction
    - for synchronous unresectable metastases of other sites
    - as primary treatment for unresectable metachronous metastases in patients who have not received previous adjuvant FOLFOX or CapeOX within the past 12 months, who have received previous fluorouracil/leucovorin (5-FU/LV) or capecitabine therapy, or who have not received any previous chemotherapy
    - for unresectable metachronous metastases that remain unresectable after primary treatment and progressed on non-intensive therapy, except if received previous fluoropyrimidine, with improvement in functional status
    - Subsequent therapy in combination with nivolumab (if no previous treatment with a checkpoint inhibitor) for advanced or metastatic disease following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy

Recommended dosage: Ipilimumab 1 mg/kg on the same day every 3 weeks for 4 doses given in combination with nivolumab, then nivolumab monotherapy.

Hepatocellular Carcinoma

- The member will be using ipilimumab as subsequent treatment in combination with nivolumab (Child-Pugh Class A only) for progressive disease in patients and
    - have unresectable disease and are not a transplant candidate
    - have liver-confined disease, inoperable by performance status, comorbidity or with minimal or uncertain extrahepatic disease
    - have metastatic disease or extensive liver tumor burden

Recommended dosage: Ipilimumab 3 mg/kg on the same day every 3 weeks for 4 doses in combination with nivolumab, followed by nivolumab monotherapy

Non-Small Cell Lung Cancer (NSCLC)

- The member will be using ipilimumab as treatment for recurrent, advanced, or metastatic disease in combination with
    - Nivolumab **OR**

  - Nivolumab, pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology **OR**
  - Nivolumab, paclitaxel, and carboplatin for squamous cell histology
  - The above regimens are used as:
    - initial systemic therapy for PD-L1 <1% and negative for actionable molecular markers
    - first-line therapy for EGFR exon 20 mutation positive tumors
    - first-line therapy for KRAS G12C mutation positive tumors
    - first-line (useful in certain circumstances) or subsequent therapy for BRAF V600E mutation positive tumors
    - first-line (useful in certain circumstances) or subsequent therapy for NTRK1/2/3 gene fusion positive tumors
    - first-line (useful in certain circumstances) or subsequent therapy for MET exon 14 skipping mutation positive tumors
    - subsequent therapy for ROS1 rearrangement positive tumors and prior crizotinib, entrectinib, or ceritinib therapy
- The member will be using ipilimumab as continuation maintenance therapy in combination with nivolumab for recurrent, advanced, or metastatic disease in patients who achieve a response or stable disease following first-line therapy if nivolumab + ipilimumab +/- chemotherapy given:
  - PD-L1 expression positive (≥1%) tumors that are negative for actionable molecular markers **OR**
  - PD-L1 expression <1% and no contraindications to PD-1 or PD-L1 inhibitors

Recommended dosage: Ipilimumab 1 mg/kg on day 1 in combination with nivolumab +/- chemotherapy every 42 day cycle

Central Nervous System (CNS) Lesions-Metastatic Melanoma

- The member has a diagnosis of limited brain metastases with melanoma for **ANY** of the following:
  - Ipilimumab will be administered in combination with nivolumab for newly diagnosed brain metastases in select individuals (e.g., with small asymptomatic brain metastases) and stable systemic disease or reasonable systemic treatment options; **OR**
  - Ipilimumab will be administered in combination with nivolumab for recurrent brain metastases; **or**
  - Ipilimumab will be administered as a single agent for recurrent brain metastases; **OR**
- The member has recurrent extensive brain metastases with melanoma and stable systemic disease or reasonable systemic treatment options for **ANY** of the following:
  - Ipilimumab will be administered in combination with nivolumab; **OR**
  - Ipilimumab will be administered as a single agent

Recommended dosage:

- Single Agent: Initial dose 10 mg/kg every 3 weeks for 4 doses then 10 mg/kg every 12 weeks
- Combination with nivolumab: Initial dose 3 mg/kg every 3 weeks given with nivolumab followed nivolumab monotherapy.

Malignant Pleural Mesothelioma

- The member will be using ipilimumab in combination with nivolumab (preferred for biphasic or sarcomatoid histology, other recommended regimen for epithelioid histology) as first-line systemic therapy for
  - unresectable clinical stage I-IIIA disease and epithelioid or biphasic histology **OR**
  - clinical stage IIIB or IV disease, sarcomatoid, or medically inoperable tumors in patients with performance status (PS) 0-2
- The member will be using Ipilimumab as subsequent systemic therapy in combination with nivolumab

Recommended dosage: Ipilimumab 1 mg/kg on day 1 in combination with nivolumab +/- chemotherapy every 42 day cycle

Small Bowel Adenocarcinoma

- The member will be using Ipilimumab in combination with nivolumab for advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) for **ANY** of the following:
  - Initial therapy in combination with nivolumab for advanced or metastatic disease, if no previous treatment with a checkpoint inhibitor **OR**
  - Subsequent therapy in combination with nivolumab for advanced or metastatic disease, if no previous treatment with a checkpoint inhibitor and no prior oxaliplatin exposure in the adjuvant setting or contraindication to oxaliplatin

Recommended dosage: Ipilimumab 1 mg/kg every 3 weeks for a total of 4 doses given in combination with nivolumab followed by nivolumab monotherapy.

All indications:

- Ipilimumab will be approved through clinical review for up to a 6-month duration

Coverage Limitations

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

- The member has had prior treatment with an anti-Programmed Death receptor-1 (PD-1), anti-Programmed Death-1 ligand-1 (PD-L1), anti-PD-L2, or anti-cytotoxic T lymphocyte associated antigen-4 (anti-CTLA-4) antibody
- Indications not supported by NCCN category 2A or higher 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 toxicities including but not limited to:
        - Hepatitis
        - Endocrinopathies
        - Pneumonitis
        - Nephritis and renal dysfunction
        - Encephalitis
    - Infusion reactions
    - Embryo-Fetal toxicity

For specific recommendations on contraindications, warnings and precautions, patient monitoring, and on dose adjustments and discontinuation, please refer to the current prescribing information.

Billing

- **Description:** Injection, ipilimumab, 1 mg
    - HCPCS: J9228

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

1. Yervoy [package insert]. Bristol-Myers Squibb Co, Princeton, NJ. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf
2. Yervoy. NCCN Drugs & Biologics Compendium. Available at:

https://packageinserts.bms.com/pi/pi_yervoy.pdf
3. Tarhini AA, Lee SJ, Hodi FS, et al. Phase III Study of Adjuvant Ipilimumab (3 or 10mg/kg) versus High-Dose interferon Alfa-2b for Resected High Risk Melanoma: North American Intergroup E1609. J Clin Oncol. Feb 20; 38 (6): 567-575.
4. Opdivo [package insert]. Bristol-Myers Squibb Co, Princeton, NJ. Available at: https://packageinserts.bms.com/pi/pi_opdivo.pdf
5. Momtaz P, Park V, Panageas KS et al. Safety of Infusing Ipilimumab Over 30 Minutes. J Clin Oncol. 2015 Oct 20; 33(30): 3454-3458.
6. MDX-010 Antibody, MDX-1379 Melanoma Vaccine, or MDS-010/MDS-1379 Combination Treatment for Patients with Unresectable or Metastatic Melanoma. Available at: https://clinicaltrials.gov/ct2/show/NCT00094653
7. Coens,C, Suciu, S, Chiarian-Sileni V, et al. Health-related quality of life with adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): secondary outcomes of a multinational, randomised, double-blind, phase 3 trial. Lancet Oncol. 2017 Mar 18;(3):393-403.
8. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010 Aug 19;363(8):711-723.
9. Efficacy Study of Ipilimumab Versus Placebo to Prevent Recurrence After Complete Resection of High Risk Stage III Melanoma. Available at: https://clinicaltrials.gov/ct2/show/results/NCT00636168?view=results
10. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol. 2015 May; 16(5):522-530.
11. Nivolumab Combined With Ipilimumab Versus Sunitinib in Previously Untreated Advanced or Metastatic Renal Cell Carcinoma (CheckMate 214). Available at: https://clinicaltrials.gov/ct2/show/NCT02231749
12. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma. N Engl J Med. 2018 Apr 5;378(14): 1277-1290.
13. An Investigational Immuno-therapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread (CheckMate142). Available at: https://clinicaltrials.gov/ct2/show/NCT02060188
14. Overman MJ, Lonardi S, Wong KYM, et al. Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair-Deficient/Microsatellite Instability-High Metastatic Colorectal Cancer. J Clin Oncol. 2018 Mar 10;36(8):773-779.
15. FDA grants accelerated approval to ipilimumab for MSI-H or dMMR metastatic colorectal cancer. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-ipilimumab-msi-h-or-dmmr-metastatic-colorectal-cancer
16. An Investigational Immuno-therapy Trial of Nivolumab, or Nivolumab Plus Ipilimumab, or Nivolumab Plus Platinum-doublet Chemotherapy, Compared to Platinum Doublet Chemotherapy in Patients With Stage IV Non-Small Cell Lung Cancer (NSCLC) (CheckMate 227). Available at: https://clinicaltrials.gov/ct2/show/NCT02477826
17. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. N Engl J Med. 2018 May 31;378(22):2093-2104.
18. Hellmann, MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in Advanced Non-Small-Cell Lung Cancer. N Engl J Med. 2019 Nov 21;381(21):2020-2031.
19. Ipilimumab and Nivolumab in the Treatment of Malignant Pleural Mesothelioma (INITIATE). Available at: https://clinicaltrials.gov/ct2/show/NCT03048474
20. Disselhorst MJ, Quispel-Janssen J, Lalezari F, et al. Ipilimumab and nivolumab in the treatment of recurrent malignant pleural mesothelioma (INITIATE): results of prospective, single-arm phase 2 trial. The Lancet. 2019 Mar 01;7(3):260-270.
21. Nivolumab and Ipilimumab in Treating Patients With Metastatic Uveal Melanoma. Available at:

https://www.clinicaltrials.gov/ct2/show/NCT01585194
22. Pelster M, Gruschkus S, Bassett R, et al. Phase II study of ipilimumab and nivolumab (ipi/nivo) in metastatic uveal melanoma (UM). J Clin Oncol. 2019 37:15_suppl, 9522-9522.
23. A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01928394
24. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol. 2016 Jul;17(7):883-895.
25. Nivolumab and Ipilimumab in Treating Patients With Rare Tumors. Available at: https://clinicaltrials.gov/ct2/show/NCT02834013
26. AACR: Bristol-Myers Squibb's Opdivo-Yervoy duo provokes response in rare tumors. Available at: https://www.fiercepharma.com/pharma/aacr-bristol-myers-squibb-s-opdivo-yervoy-duo-provokes-response-rare-tumors
27. An Immuno-therapy Study to Evaluate the Effectiveness, Safety and Tolerability of Nivolumab or Nivolumab in Combination With Other Agents in Patients With Advanced Liver Cancer (CheckMate040). Available at: https://clinicaltrials.gov/ct2/show/NCT01658878