Ipilimumab (Yervoy®)

IMPORTANT REMINDER

We develop Medical Policies to provide guidance to Members and Providers. This Medical Policy relates only to the services or supplies described in it. The existence of a Medical Policy is not an authorization, certification, explanation of benefits or a contract for the service (or supply) that is referenced in the Medical Policy. For a determination of the benefits that a Member is entitled to receive under his or her health plan, the Member's health plan must be reviewed. If there is a conflict between the medical policy and a health plan or government program (e.g., TennCare), the express terms of the health plan or government program will govern.

The proposal is to add text/statements in red and to delete text/statements with strikethrough:

POLICY

INDICATIONS

The indications below including FDA-approved indications and compendial uses are considered a covered benefit provided that all the approval criteria are met and the member has no exclusions to the prescribed therapy.

FDA-Approved Indications

Unresectable or Metastatic Melanoma
Yervoy is indicated as a single agent or in combination with nivolumab for the treatment of unresectable or metastatic melanoma in adult and pediatric patients 12 years and older.

Adjuvant Treatment of Melanoma
Yervoy is indicated for the adjuvant treatment of adult patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Advanced Renal Cell Carcinoma
Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma (RCC).

Microsatellite Instability-High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer
Yervoy, in combination with nivolumab, is indicated for the treatment of adult and pediatric patients 12 years of age and older with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer (CRC).

Hepatocellular Carcinoma

- Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable or metastatic hepatocellular carcinoma (HCC).

- Yervoy, in combination with nivolumab, is indicated for the treatment of adult patients with unresectable or metastatic HCC who have been previously treated with sorafenib.

Metastatic Non-small Cell Lung Cancer

- Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations.

- Yervoy, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, is indicated for the first-line treatment of adult patients with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations.

Malignant Pleural Mesothelioma
Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma.

Esophageal Cancer
Yervoy, in combination with nivolumab, is indicated for the first-line treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC) whose tumors express PD-L1 (≥1).

Compendial Uses

- Cutaneous melanoma
- Uveal melanoma
- Gestational trophoblastic neoplasia
- Central nervous system (CNS) brain metastases
- Non-small cell lung cancer
- Renal cell carcinoma
- Colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma
- Pleural mesothelioma
- Peritoneal mesothelioma
- Hepatocellular carcinoma
- Small bowel adenocarcinoma
- Ampullary adenocarcinoma
- Esophageal/Esophagogastric Junction Cancers
- Kaposi Sarcoma
- Bone Cancer
- Biliary Tract Cancers
  - Cholangiocarcinoma
  - Gallbladder Cancer
- Soft Tissue Sarcoma
  - Extremity/body wall sarcoma
  - Head/neck sarcoma
  - Retroperitoneal/intra-abdominal sarcoma
  - Rhabdomyosarcoma
  - Angiosarcoma
- Merkel Cell Carcinoma
- Gastric Cancer

All other indications are considered experimental/investigational and not medically necessary.

DOCUMENTATION

Submission of the following information is necessary to initiate the prior authorization review:

- Documentation of laboratory report confirming MSI-H, mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
- Documentation of molecular testing for EGFR alterations and ALK, RET, and ROS1 rearrangements, where applicable.

COVERAGE CRITERIA

Cutaneous Melanoma

Authorization of 6 months may be granted for treatment of cutaneous melanoma in any of the following settings:

- The requested medication will be used as a single agent (for up to 4 doses) or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for metastatic or unresectable disease.
- The requested medication will be used as a single agent (for up to 8 doses) or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) as adjuvant treatment if no evidence of disease following systemic or metastasis-directed therapy (e.g., complete resection).
- The requested medication will be used at a low dose in combination with pembrolizumab for disease progression following anti- PD-1 therapy as subsequent therapy for metastatic or unresectable disease.
- The requested medication will be used as a single agent (for up to 8 doses) for resectable disease after prior anti-PD-1 therapy.
- The requested medication will be used in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) as neoadjuvant treatment.

Uveal Melanoma

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of uveal melanoma for unresectable or metastatic disease.

Gestational Trophoblastic Neoplasia

Authorization of 6 months may be granted in combination with nivolumab for treatment of gestational trophoblastic neoplasia for multi-agent chemotherapy-resistant disease when either of the following criteria is are met:

- Member has recurrent or progressive intermediate trophoblastic tumor (placental site trophoblastic tumor or epithelioid trophoblastic tumor).
- Member has high-risk disease.

CNS Brain Metastases

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of CNS brain metastases in members with melanoma.

Non-Small Cell Lung Cancer (NSCLC)

Authorization of 6 months may be granted for treatment of recurrent, advanced or metastatic non-small cell lung cancer if there are no EGFR exon 19 deletions or exon 21 L858R mutations or ALK, RET, or ROS1 rearrangements (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing nivolumab.

Renal Cell Carcinoma

Authorization of 6 months may be granted for treatment of renal cell carcinoma in combination with nivolumab (for 4 doses, followed by single agent nivolumab) for relapsed, advanced, or stage IV disease with clear cell histology.

Colorectal Cancer

Authorization of 6 months may be granted for treatment of colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma, for microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) >50 mut/Mb) when used in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

Pleural or Peritoneal Mesothelioma

Authorization of 6 months may be granted in combination with nivolumab for treatment of pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma.

Hepatocellular Carcinoma

Authorization of 6 months may be granted for treatment of hepatocellular carcinoma in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for either of the following:

- First-line treatment of unresectable or extrahepatic/metastatic disease
- Subsequent treatment

Small Bowel Adenocarcinoma

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of unresectable, medically inoperable, advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H), mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors with ultra-hypermutated phenotype (e.g., tumor mutational burden (TMB) > 50 mut/Mb).

Ampullary Adenocarcinoma

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of progressive, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma.

Esophageal and Esophagogastric Junction Cancers

- Authorization of 6 months may be granted in combination with nivolumab for the treatment of esophageal or esophagogastric junction cancer in members who are not surgical candidates or have unresectable locally advanced, recurrent or metastatic disease and PD-L1 ≥ 1.
- Authorization of 6 months may be granted in combination with nivolumab for treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).
- Authorization of 6 months may be granted for induction therapy for relieving dysphagia in combination with nivolumab for members with PD-L1 ≥ 1 planned for esophagectomy.

Gastric Cancer

Authorization of 6 months may be granted in combination with nivolumab for treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).

Kaposi Sarcoma

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of relapsed/refractory Kaposi Sarcoma.

Bone Cancer

Authorization of 6 months may be granted in combination with nivolumab for unresectable or metastatic disease when all of the following are met:

- Disease has tumor mutation burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] tumors
- Disease has progressed following prior treatment and has no satisfactory alternative treatment options

Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of unresectable or resected gross residual (R2) disease, or metastatic disease that is tumor mutation burden-high (TMB-H).

Authorization of 6 months may be granted in combination with nivolumab for neoadjuvant treatment of resectable locoregionally advanced gallbladder cancer that is tumor mutation burden-high (TMB-H) when disease does not present as jaundice.

Soft Tissue Sarcoma

Authorization of 6 months may be granted in combination with nivolumab for treatment of extremity/body wall sarcomas, head/neck sarcomas and retroperitoneal/intra-abdominal sarcomas, rhabdomyosarcoma and angiosarcoma.

Merkel Cell Carcinoma

Authorization of 6 months may be granted as a single agent or in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for treatment of primary node positive regional, unresectable, recurrent, or stage IV Merkel cell carcinoma.

CONTINUATION OF THERAPY

Adjuvant Treatment of Melanoma

Authorization of 6 months may be granted (up to 3 years) for continued treatment in members requesting reauthorization for adjuvant melanoma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

Cutaneous Melanoma, Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Cancer
Authorization of 6 months may be granted (up to 4 doses maximum, if member has not already received 4 doses) for continued treatment in members requesting reauthorization for cutaneous melanoma, renal cell carcinoma, colorectal cancer, and hepatocellular cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

Non-Small Cell Lung Cancer, Gastric/Esophageal/Esophagogastric Junction Cancers, or Pleural Mesothelioma

Authorization of 6 months may be granted (up to 24 months total) for continued treatment in members requesting reauthorization for non-small cell lung cancer, esophageal cancer, or pleural mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes, when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

Biliary Tract Cancer

Authorization of 6 months may be granted (for 2 to 6 months total for neoadjuvant treatment, and for up 24 months total for other clinical settings) for continued treatment in members requesting reauthorization for biliary tract cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

All Other Indications

Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for all other indications listed in the Coverage Criteria section when treatment guidelines do not specify a limited number of total doses (see above) and there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

MEDICATION QUANTITY LIMITS

Drug Name	Diagnosis	Maximum Dosing Regimen
Yervoy (Ipilimumab)	Ampullary Adenocarcinoma	Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses
Yervoy (Ipilimumab)	Biliary Tract Cancer: Gallbladder Cancer, Cholangiocarcinoma	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Bone Cancer	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	CNS Cancer: Brain Metastases	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses Initial: 10mg/kg every 3 weeks for 4 doses Maintenance: 10mg/kg every 12 weeks beginning with week 24
Yervoy (Ipilimumab)	Colorectal Cancer, including Appendiceal Adenocarcinoma and Anal Adenocarcinoma	Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses
Yervoy (Ipilimumab)	Esophageal Cancer, Esophagogastric Junction Cancer	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Gastric Cancer	Route of Administration: Intravenous 1mg/kg every 6 weeks for 2-3 doses
Yervoy (Ipilimumab)	Gestational Trophoblastic Neoplasia	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Hepatocellular Carcinoma	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses
Yervoy (Ipilimumab)	Kaposi Sarcoma	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Melanoma	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses

Yervoy (Ipilimumab)	Melanoma Cutaneous, Adjuvant	Route of Administration: Intravenous Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 3mg/kg every 12 weeks up to max 4 doses
Yervoy (Ipilimumab)	Merkel Cell Carcinoma	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses
Yervoy (Ipilimumab)	Mesothelioma (Pleural, Peritoneal, Pericardial, or Tunica Vaginalis Testis)	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Non-Small Cell Lung Cancer (NSCLC)	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Renal Cell Carcinoma	Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses
Yervoy (Ipilimumab)	Small Bowel Adenocarcinoma	Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses
Yervoy(Ipilimumab)	Soft Tissue Sarcoma: Angiosarcoma, Extremity/Body Wall Sarcoma, Head/Neck Sarcoma, Retroperitoneal/Intra-Abdominal Sarcoma, Rhabdomyosarcoma	Route of Administration: Intravenous 1mg/kg every 6 weeks

~~Drug Name~~	~~Diagnosis~~	~~Maximum Dosing Regimen~~
~~Yervoy (Ipilimumab)~~	~~Ampullary Adenocarcinoma, Colorectal Cancer including Appendiceal Adenocarcinoma and Anal Adenocarcinoma, Renal Cell Carcinoma, Small Bowel Adenocarcinoma~~	~~Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses~~
~~Yervoy (Ipilimumab)~~	~~Biliary Tract Cancer: Gallbladder Cancer, Cholangiocarcinoma, Bone Cancer, Kaposi Sarcoma, Mesothelioma (Pleural, Peritoneal, Pericardial, or Tunica Vaginalis Testis), Non-Small Cell Lung Cancer~~	~~Route of Administration: Intravenous 1mg/kg every 6 weeks~~
~~Yervoy (Ipilimumab)~~	~~CNS Cancer : Brain Metastases~~	~~Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses Initial: 10mg/kg every 3 weeks for 4 doses Maintenance: 10mg/kg every 12 weeks beginning with week 24~~
~~Yervoy (Ipilimumab)~~	~~Esophageal Cancer, Esophagogastric Junction Cancer~~	~~Route of Administration: Intravenous 1mg/kg every 6 weeks~~
~~Yervoy (Ipilimumab)~~	~~Gastric Cancer~~	~~Route of Administration: Intravenous 1mg/kg every 6 weeks for 2-3 doses~~

~~Yervoy (Ipilimumab)~~	~~Hepatocellular Carcinoma, Melanoma~~	~~Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses~~
~~Yervoy (Ipilimumab)~~	~~Melanoma Cutaneous, Adjuvant~~	~~Route of Administration: Intravenous Initial: 3mg/kg every 3 weeks for 4 doses Maintenance: 3mg/kg every 12 weeks up to max 4 doses~~
~~Yervoy (Ipilimumab)~~	~~Merkel Cell Carcinoma~~	~~Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses~~
~~Yervoy (Ipilimumab)~~	~~Soft Tissue Sarcoma: Angiosarcoma, Extremity/Body Wall Sarcoma, Head/Neck Sarcoma, Retroperitoneal/Intra-Abdominal Sarcoma, Rhabdomyosarcoma~~	~~Route of Administration: Intravenous 1mg/kg every 6 weeks~~

APPLICABLE TENNESSEE STATE MANDATE REQUIREMENTS

BlueCross BlueShield of Tennessee's Medical Policy complies with Tennessee Code Annotated Section 56-7-2352 regarding coverage of off-label indications of Food and Drug Administration (FDA) approved drugs when the off-label use is recognized in one of the statutorily recognized standard reference compendia or in the published peer-reviewed medical literature.

ADDITIONAL INFORMATION

For appropriate chemotherapy regimens, dosage information, contraindications, precautions, warnings, and monitoring information, please refer to one of the standard reference compendia (e.g., the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) published by the National Comprehensive Cancer Network®, Drugdex Evaluations of Micromedex Solutions at Truven Health, or The American Hospital Formulary Service Drug Information).

REFERENCES

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3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 2.2025. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 19, 2025.
4. Lexicomp [database online]. Hudson, OH: Lexi-Comp, Inc.; https://online.lexi.com/lco/action/home [available with subscription]. Accessed March 19, 2025.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer Version 1.2025.https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf Accessed March 19, 2025.

EFFECTIVE DATE

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