Draft Revision Policy: Do Not Implement

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 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

- Adrenal Gland Tumors
- Ampullary adenocarcinoma
- Appendiceal neoplasms and cancers
- Biliary Tract Cancers
  - Cholangiocarcinoma
  - Gallbladder Cancer
- Bone Cancer
- Central nervous system (CNS) brain metastases
- Cervical Cancer
- Colorectal cancer, including anal adenocarcinoma
- Cutaneous melanoma
- Esophageal/Esophagogastric Junction Cancers
- Gastric Cancer
- Gestational trophoblastic neoplasia
- Hepatocellular carcinoma
- Kaposi Sarcoma
- Merkel Cell Carcinoma
- Non-small cell lung cancer
- Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer
- Peritoneal mesothelioma
- Pleural mesothelioma
- Renal cell carcinoma
- Small bowel adenocarcinoma
- Soft Tissue Sarcoma
  - Angiosarcoma
  - Borderline/malignant phyllodes tumor of the breast
  - Dedifferentiated liposarcoma
  - Epithelioid hemangioendothelioma
  - Extremity/body wall sarcoma
  - Head/neck sarcoma
  - Pleomorphic rhabdomyosarcoma
  - Retroperitoneal/intra-abdominal sarcoma
- Uterine Neoplasms
  - Endometrial Carcinoma
  - Uterine Sarcoma
- Uveal Melanoma
- Vaginal Cancer
- Vulvar 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 microsatellite instability-high (MSI-H), mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
- Documentation of the absence of EGFR exon 19 deletion and exon 21 L858R mutations, ALK, RET, and ROS1 gene fusions, where applicable.

COVERAGE CRITERIA

Adrenal Gland Tumors

Authorization of 6 months may be granted in combination with nivolumab for treatment of unresectable or metastatic adrenocortical carcinoma.

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.

Appendiceal Neoplasms and Cancers

Authorization of 6 months may be granted for treatment of appendiceal neoplasms and appendiceal cancers (including appendiceal adenocarcinoma, goblet cell adenocarcinoma, and undifferentiated carcinoma not otherwise specified) 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).

Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of unresectable or gross residual (R2), or metastatic extrahepatic or intrahepatic cholangiocarcinoma or gallbladder cancer that is tumor mutational 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 mutational burden-high (TMB-H).

Bone Cancer

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

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

Central Nervous System 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 BRAF non-specific melanoma.

Cervical Cancer

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of cervical cancer when either of the following criteria is met:

- Disease is recurrent or metastatic.
- Disease is persistent small cell neuroendocrine carcinoma of the cervix (NECC).

Colorectal Cancer

Authorization of 6 months may be granted for treatment of colorectal cancer, including 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).

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 in combination with nivolumab (for up to 4 doses followed by nivolumab as a single agent) as adjuvant treatment of oligometastatic disease if no evidence of disease following systemic or metastasis-directed therapy (e.g., complete resection).
- The requested medication will be used as a single agent (for up to 8 doses) as adjuvant treatment of local satellite/in-transit recurrence, resectable, or oligometastatic disease after prior anti-PD-1 therapy.
- The requested medication will be used at a low dose in combination with pembrolizumab (for up to 4 doses followed by pembrolizumab as a single agent) for disease progression following anti- PD-1 therapy as subsequent therapy for metastatic or unresectable disease.
- The requested medication will be used in combination with nivolumab (for up to 2 doses followed by nivolumab as a single agent) as neoadjuvant treatment.

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 when either of the following criteria is met:

- First-line therapy when PD-L1 ≥ 1.
- Subsequent therapy.

Authorization of 6 months may be granted in combination with nivolumab for treatment of esophageal or esophagogastric junction cancer 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 esophageal or esophagogastric junction squamous cell carcinoma 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).

Gestational Trophoblastic Neoplasia

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

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

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.

Kaposi Sarcoma

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

Merkel Cell Carcinoma

Authorization of 6 months may be granted as a single agent or in combination with nivolumab for treatment of regional, in-transit, unresectable, recurrent, or stage IV Merkel cell carcinoma.

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 gene fusions (unless testing is not feasible due to insufficient tissue) and the requested medication will be used in a regimen containing nivolumab.

Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer

Authorization of 6 months may be granted in combination with nivolumab for treatment of progressive, persistent, or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer, clear cell carcinoma of the ovary, and hypercalcemic type small cell carcinoma of the ovary.

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.

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.

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).

Authorization of 6 months may be granted in combination with nivolumab (for 4 doses followed by nivolumab as a single agent) for neoadjuvant treatment of 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).

Soft Tissue Sarcoma

Authorization of 6 months may be granted in combination with nivolumab for treatment of pleomorphic rhabdomyosarcoma, borderline/malignant phyllodes tumor of the breast, and epithelioid hemangioendothelioma that is tumor mutational burden-high (TMB-H) [≥10 mut/Mb].

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

Uterine Neoplasms

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of recurrent unresectable or metastatic endometrial carcinoma that is tumor mutational burden-high (TMB-H) [≥10 mut/Mb] and has no satisfactory alternative treatment options.

Authorization of 6 months may be granted in combination with nivolumab for subsequent treatment of unresectable or metastatic uterine sarcoma that is tumor mutational burden-high (TMB-H) [≥10 mut/Mb] and has no satisfactory alternative treatment options.

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.

Vaginal Cancer

Authorization of 6 months may be granted as subsequent therapy for recurrent or metastatic vaginal cancer when used in combination with nivolumab.

Vulvar Cancer

Authorization of 6 months may be granted as subsequent therapy for advanced or recurrent/metastatic vulvar cancer when used in combination with nivolumab.

CONTINUATION OF THERAPY

AMPULLARY ADENOCARCINOMA, APPENDICEAL NEOPLASMS AND CANCERS, COLORECTAL CANCER, HEPATOCELLULAR CANCER, RENAL CELL CARCINOMA, SMALL BOWEL ADENOCARCINOMA, OR UVEAL MELANOMA

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 ampullary adenocarcinoma, appendiceal neoplasms and cancers, colorectal cancer, hepatocellular cancer, renal cell carcinoma, small bowel adenocarcinoma, and uveal melanoma 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 to 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.

Bone Cancer, Cervical Cancer, Esophageal/Esophagogastric Junction Cancers, Kaposi Sarcoma, Non-Small Cell Lung Cancer, Pleural or Peritoneal Mesothelioma, Soft Tissue Sarcoma, Uterine Neoplasms, Vaginal Cancer, or Vulvar Cancer

Authorization of 6 months may be granted (up to 24 months total) for continued treatment in members requesting reauthorization for bone cancer, cervical cancer, esophageal/esophagogastric junction cancer, Kaposi sarcoma, non-small cell lung cancer, pleural or peritoneal mesothelioma, including pericardial mesothelioma and tunica vaginalis testis mesothelioma subtypes, soft tissue sarcoma, uterine neoplasms, vaginal cancer, or vulvar cancer when there is no evidence of unacceptable toxicity or disease progression while on the current regimen.

Cutaneous Melanoma

Authorization of 6 months may be granted for continued treatment when the requested medication requesting reauthorization for cutaneous melanoma when there is no evidence of unacceptable toxicity or disease progression while on the current regimen for either of the following durations of therapy:

- Up to 8 doses maximum, if member has not already received 8 doses, and the requested medication will be used as single agent for adjuvant treatment of local satellite/in-transit recurrence, resectable, or oligometastatic disease.
- Up to 4 doses maximum, if member has not already received 4 doses, and one of the following is met:
  - The requested medication will be used in combination with nivolumab for adjuvant treatment.
  - The requested medication will be used as neoadjuvant treatment.
  - The requested medication will be used as a single agent, in combination with pembrolizumab or nivolumab and member has metastatic or unresectable disease.
- Up to 2 doses maximum, if member has not already received 2 doses, and the requested medication will be used as neoadjuvant treatment.

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)	Adrenal Gland Tumors	Route of Administration: Intravenous 1mg/kg every 6 weeks
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)	Cervical Cancer	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses 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 Neoplasms ~~Adenocarcinoma~~ and Cancers 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)	Ovarian, Fallopian, Primary Peritoneal Cancer	Route of Administration: Intravenous 1mg/kg every 3 weeks for 4 doses 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 3 weeks for 4 doses 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Uterine Neoplasms including Endometrial Carcinoma and Uterine Sarcoma	Route of Administration: Intravenous 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Vaginal Cancer	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Vulvar Cancer	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 doses 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

1. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; May 2025.
2. The NCCN Drugs & Biologics Compendium® © 2026 National Comprehensive Cancer Network, Inc. Available at: http://www.nccn.org. Accessed March 4, 2026.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Anal Carcinoma. Version 1.2026. https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf Accessed March 4, 2026.
4. Lexicomp Online, Lexi-Drugs Online. Waltham, MA: UpToDate, Inc.; 2026 http://online.lexi.com. Accessed March 4, 2026.
5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer Version 2.2026.https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf Accessed March 4, 2026.
6. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Appendiceal Neoplasms and Cancers Version 1.2026. https://www.nccn.org/professionals/physician_gls/pdf/appendiceal.pdf Accessed March 4, 2026.

EFFECTIVE DATE

ID_CHS_17962026a_1026