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.

POLICY

I. 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.

A. FDA-Approved Indications

1. 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.

2. 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.

3. 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).

4. 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 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.

5. Hepatocellular Carcinoma
   Yervoy, in combination with nivolumab, is indicated for the treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib.

6. Metastatic Non-small Cell Lung Cancer
   a. 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.
   b. 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.

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

8. 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).

B. Compendial Uses
1. Cutaneous melanoma
2. Uveal melanoma
3. Central nervous system (CNS) brain metastases
4. Non-small cell lung cancer
5. Renal cell carcinoma
6. Colorectal cancer, including appendiceal adenocarcinoma and anal adenocarcinoma
7. Pleural mesothelioma
8. Peritoneal mesothelioma
9. Hepatocellular carcinoma
10. Small bowel adenocarcinoma
11. Ampullary adenocarcinoma
12. Esophageal/Esophagogastric Junction Cancers
13. Kaposi Sarcoma
14. Bone Cancer
15. Biliary Tract Cancers
    a. Cholangiocarcinoma
    b. Gallbladder Cancer
16. Soft Tissue Sarcoma
    a. Extremity/body wall sarcoma
    b. Head/neck sarcoma
    c. Retroperitoneal/intra-abdominal sarcoma
    d. Rhabdomyosarcoma
    e. Angiosarcoma
17. Merkel Cell Carcinoma
18. Gastric Cancer

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

II. DOCUMENTATION

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

A. Documentation of laboratory report confirming MSI-H or mismatch repair deficient (dMMR), or polymerase epsilon/delta (POLE/POLD1) tumor status, where applicable.
B. Documentation of molecular testing for EGFR exon 19 deletions or exon 21 L858R mutations and ALK rearrangements, where applicable

III. CRITERIA FOR INITIAL APPROVAL

A. Cutaneous Melanoma

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

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

B. 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.

C. 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.

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

E. 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.

F. 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) or mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors when used in combination with nivolumab (for 4 doses followed by nivolumab as a single agent).

G. 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.

H. Hepatocellular Carcinoma

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

I. 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 advanced or metastatic small bowel adenocarcinoma for microsatellite-instability high (MSI-H), or mismatch repair deficient (dMMR) or polymerase epsilon/delta (POLE/POLD1) tumors.

J. 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, unresectable, or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) ampullary adenocarcinoma.

K. Esophageal and Esophagogastric Junction Cancers

1. 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.
2. Authorization of 6 months may be granted in combination with nivolumab for neoadjuvant or perioperative treatment of esophageal or esophagogastric junction adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.

L. Gastric Cancer

1. Authorization of 6 months may be granted in combination with nivolumab for treatment of gastric adenocarcinoma in members with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors who are not surgical candidates or have unresectable, recurrent or metastatic disease.
2. Authorization of 6 months may be granted in combination with nivolumab for neoadjuvant or perioperative treatment of gastric adenocarcinoma if tumor is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and member is medically fit for surgery.
3. When the requested medication will be used in combination with nivolumab in members with early stage microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) tumors and completed endoscopic resection.

M. Kaposi Sarcoma

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

N. 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:

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

O. Biliary Tract Cancer (Cholangiocarcinoma and Gallbladder Cancer)

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

P. 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.

Q. 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 unresectable, recurrent, or stage IV Merkel cell carcinoma.

IV. CONTINUATION OF THERAPY

A. 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.

B. 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.

C. 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.

D. All Other Indications
Authorization of 6 months may be granted for continued treatment in members requesting reauthorization for all other indications listed in Section III 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, Colorectal Cancer or Appendiceal 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)	Central Nervous System (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 Squamous Cell Carcinoma	Route of Administration: Intravenous ≥18 Years 1mg/kg every 6 weeks
Yervoy (Ipilimumab)	Gastric Cancer	Route of Administration: Intravenous 3mg/kg every 3 weeks for 4 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: 10mg/kg every 3 weeks for 4 doses Maintenance: 10mg/kg every 12 weeks
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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EFFECTIVE DATE 12/3/2024

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