Ipilimumab

NDC CODE(S) 00003-2327-XX YERVOY 50MG/10ML Solution (B-M SQUIBB U.S. (PRIMARY CARE)
00003-2328-XX YERVOY 200MG/40ML Solution (B-M SQUIBB U.S. (PRIMARY CARE)

DESCRIPTION

Ipilimumab (Yervoy®) is a recombinant human monoclonal antibody and an IgG1 kappa immunoglobulin. It binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a negative regulator of T-cell activation, and blocks interaction with its ligands CD80/CD86. Ipilimumab's mechanism of action is likely through T-cell mediated anti-tumor immune responses. Ipilimumab has been proven to be effective in crossing the blood brain barrier

POLICY

- Ipilimumab is considered ***medically necessary*** for the treatment for the following if the medical appropriateness criteria are met: **(See Medical Appropriateness below.)**
  - Central nervous system cancer
  - Hepatocellular Carcinoma
  - Malignant Pleural Mesothelioma
  - Melanoma, Cutaneous/Uveal
  - Microsatellite Instability-High (MSI-H)/Mismatch Repair Deficient (dMMR) Colorectal Cancer
  - Non-Small Cell Cancer (NSCLC)
  - Renal Cell Carcinoma (RCC)
  - Small Bowel Adenocarcinoma (SBA)
- Ipilimumab for the treatment of other conditions/diseases is considered ***investigational.***

MEDICAL APPROPRIATENESS

INITIAL APPROVAL

- Ipilimumab is considered **medically appropriate** if **ALL** of the following:
  - Individual is 18 years of age or older, unless otherwise indicated:
  - Diagnosis of **ANY ONE** of the following:
    - Diagnosis of Central Nervous System Cancer and **ALL** of the following:
      - Used for the treatment of brain metastases in individuals with melanoma
      - Used in combination with nivolumab or as a single agent for **ANY ONE** of the following:
        - Used as initial treatment in individuals with small asymptomatic brain metastases
        - Used for relapsed disease in individuals with limited brain metastases and stable systemic disease or reasonable treatment options
        - Individual has recurrent limited brain metastases
        - Used for recurrent disease in individuals with extensive brain metastases and stable systemic disease or reasonable systemic treatment options
    - Diagnosis of Hepatocellular Carcinoma (HCC) and **ALL** of the following:
      - Individual has locally advanced, unresectable, inoperable or metastatic disease
      - Used as subsequent therapy
      - Individual has Child-Pugh Class A disease
      - Used in combination with nivolumab

- Individual has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.)

- Diagnosis of Malignant Pleural Mesothelioma and used in combination with nivolumab for **ANY ONE** of the following:
  - Used as subsequent therapy
  - Used as first-line therapy in individuals with unresectable disease
- Diagnosis of Melanoma, Cutaneous and **ANY ONE** of the following:
  - Used as first line therapy for unresectable or metastatic disease in combination with nivolumab
  - Used for unresectable or metastatic disease previously treated with cytotoxic chemotherapy as a single agent in individuals at least 12 years of age or older
  - Used as subsequent therapy for unresectable or metastatic* disease and **ANY ONE** of the following:
    - Used after disease progression on first-line therapy or after maximum clinical benefit from BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.) and **ANY ONE** of the following:
      - Used as a single agent or in combination with nivolumab if checkpoint inhibitor immunotherapy was not previously used
      - Used as a single agent or in combination with nivolumab for individuals who progressed on single agent checkpoint inhibitor immunotherapy
    - Used for retreatment of disease as re-induction as a single agent or in combination with nivolumab in individuals who experienced disease control (i.e., complete or partial response or stable disease), from prior checkpoint inhibitor therapy but subsequently have disease progression/relapse > 3 months after treatment discontinuation and individual has completed initial induction (completion of 4 cycles within a 16 week period)
  - Used as single-agent for adjuvant therapy if **ANY ONE** of the following:
    - Individual has pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy
    - Individual has previously received anti-PD-1 therapy (e.g., nivolumab or pembrolizumab) and **ANY ONE** of the following:
      - Individual has local satellite/in-transit recurrence and has no evidence of disease (NED) after complete excision
      - Individual has undergone therapeutic lymph node dissection(TLND) and/or complete resection of nodal recurrence
      - Individual has undergone complete resection of distant metastatic disease

**Metastatic disease includes stage III clinical satellite/in transit metastases or local satellite/in-transit recurrence in individuals with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

- Diagnosis of Melanoma, Uveal and used as a single agent or in combination with nivolumab for distant metastatic disease
- Diagnosis of Microsatellite Instability-High (MSI-H)/Mismatch Repair Deficient (dMMR) Colorectal Cancer with **ALL** of the following:
  - Individual is 12 years of age or older
  - Used in combination with nivolumab
  - Disease is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) and **ANY ONE** of the following:
    - Individual has advanced or metastatic disease that has progressed following a fluoropyrimidine, oxaliplatin, and/or irinotecan regimen.

- Used as primary treatment for unresectable metastatic disease after previous adjuvant therapy with a FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or Cape OX (capecitabine and oxaliplatin) within the past 12 months

- Diagnosis of Non-Small Cell Lung Cancer (NSCLC) for **ANY ONE** of the following:
  - Individual has metastatic disease with a high tumor mutational burden (TMB)** (i.e., ≥10 mutations per megabase) and used in combination with nivolumab as first-line therapy
  - Used for recurrent, advanced or metastatic disease (excluding locoregional recurrence or symptomatic local disease without evidence of disseminated disease) or mediastinal lymph node recurrence with prior radiation therapy for **ANY ONE** of the following:
    - Used as first-line therapy in combination with nivolumab OR in combination with nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for non-squamous cell histology, paclitaxel and carboplatin for squamous cell histology, etc.) and **ANY ONE** of the following:
      - Used in individuals with PS 0-1 who have EGFR, ALK, ROS1, BRAF, MET exon 14 skipping mutation, and RET rearrangement negative*** tumors and PD-L1 <1%
      - Used in individuals with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E-mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements
      - Used in individuals with PS 0-2 for PD-L1 expression positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test (If confirmed using an immunotherapy assay-http://www.fda.gov/CompanionDiagnostics),that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET rearrangement negative***
    - Used as subsequent therapy in combination with nivolumab OR in combination with nivolumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology OR in combination with nivolumab, paclitaxel and carboplatin for squamous cell histology for **ANY ONE** of the following:
      - Used in individuals with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and received prior targeted therapy****
      - Used in individuals with PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E mutations, NTRK gene fusions, MET exon 14 skipping mutations, or RET rearrangements

  ***TMB is an evolving biomarker that may be helpful in selecting patients for immunotherapy. There is no consensus on how to measure TMB.*

  **** Note: If there is insufficient tissue to allow testing for all of the EGFR, ALK, ROS1, BRAF, MET, and RET, repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.*

- Diagnosis of Renal Cell Carcinoma (RCC) used in combination with nivolumab for clear cell histology and **ANY ONE** of the following:
  - Used as first-line therapy in individuals with advanced, relapsed or stage IV disease with poor or intermediate risk
  - Used as first line therapy in individuals with relapsed or stage IV disease with favorable risk
  - Used as subsequent therapy in individuals with relapsed or stage IV disease
- Diagnosis of Small Bowel Adenocarcinoma (SBA) with **ALL** of the following:
  - Individual has advanced or metastatic disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR)
  - Used in combination with nivolumab for **ANY ONE** of the following:
    - As subsequent therapy

- As initial therapy in individuals with prior oxaliplatin exposure in the adjuvant setting or a contraindication.

****Genomic Aberration/Mutational Driver Targeted Therapies (NOTE: *not all inclusive, refer to guidelines for appropriate use*)**
Sensitizing *EGFR* mutation-positive tumors • Afatinib • Dacomitinib • Erlotinib • Gefitinib • Osimertinib
ALK rearrangement-positive tumors • Alectinib • Brigatinib • Ceritinib • Crizotinib • Lorlatinib
ROS1 rearrangement-positive tumors • Ceritinib • Crizotinib • Entrectinib
BRAF V600E-mutation positive tumors • Dabrafenib+Trametinib • Vemurafenib
NTRK Gene Fusion positive tumors • Larotrectinib • Entrectinib
PD-1/PD-L1 expression-positive tumors (≥1%) • Pembrolizumab • Atezolizumab • Nivolumab ± ipilimumab
MET Exon-14 skipping mutations • Capmatinib • Crizotinib
RET rearrangement-positive tumors • Cabozantinib • Selpercatinib • Vandetanib

RENEWAL CRITERIA

- Ipilimumab considered **medically appropriate** for renewal if **ALL** of the following criteria are met:
  - Individual continues to meet initial approval criteria (not including prerequisite therapy)
  - Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: immune-mediated reactions (e.g. diarrhea, colitis, hepatitis, dermatitis/skin adverse reactions, neuropathies, pneumonitis, nephritis/renal dysfunction, encephalitis, endocrinopathies

[i.e. hypophysitis hypothyroidism, hyperthyroidism, adrenal insufficiency], and ocular toxicity, etc.), severe infusion reactions, complications of allogeneic hematopoietic stem cell transplant, etc.

- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread
- Coverage may not be renewed for the following indications: Renal Cell Carcinoma (RCC), Colorectal Cancer (CRC), Small Bowel Adenocarcinoma (SBA), Hepatocellular Carcinoma (HCC), Cutaneous Melanoma (excluding adjuvant therapy), Uveal Melanoma, CNS metastases from melanoma (combination therapy with nivolumab)
- Additional requirements for diagnoses of **ANY ONE** of the following:
  - Cutaneous Melanoma Re-induction as a single agent or in combination with nivolumab in individuals who experienced disease control (i.e., complete or partial response or stable disease), but subsequently have disease progression/relapse > 3 months after treatment discontinuation and individual has completed initial induction (completion of 4 cycles within a 16 week period)
  - Cutaneous Melanoma Maintenance therapy (adjuvant treatment) and individual has not exceeded a maximum of 3 years of therapy
  - Non-Small Cell Lung Cancer (NSCLC) and individual has not exceeded a maximum of two (2) years of therapy
  - MPM (initial therapy) individual has not exceeded a maximum of two (2) years of therapy

INDICATION(S)	DOSAGE & ADMINISTRATION
Cutaneous Melanoma – (excluding adjuvant therapy)	Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses
Cutaneous Melanoma – (adjuvant therapy)	Administer 10 mg/kg intravenously every 3 weeks for 4 doses, followed by 10 mg/kg intravenously every 12 weeks for up to 3 years
Uveal Melanoma	**Single Agent** Administer 3 mg/kg or 10 mg/kg intravenously every 3 weeks for 4 doses **In combination with nivolumab:** Administer 3 mg/kg intravenously 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
CNS metastases from melanoma	**Single Agent:** **Initial:** Administer 10 mg/kg intravenously every 3 weeks for 4 doses **Subsequent** (starting at week 24)**:** Administer 10 mg/kg intravenously every 12 weeks until disease progression or unacceptable toxicity **In Combination with nivolumab:** Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Hepatocellular Carcinoma (HCC)	Administer 3 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab followed by nivolumab monotherapy)
Non-Small Cell Lung Cancer (NSCLC)	**In combination with nivolumab:** Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 3 mg/kg every 2 weeks), until disease progression or unacceptable toxicity for up to 2 years **In combination with nivolumab and platinum-doublet chemotherapy:** Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab 360 mg every 3 weeks and histology-based platinum-

	doublet chemotherapy every 3 weeks for 2 cycles), until disease progression or unacceptable toxicity for up to 2 years
Renal Cell Carcinoma (RCC), Colorectal Cancer (CRC), and Small Bowel Adenocarcinoma (SBA)	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab followed by nivolumab monotherapy)
Malignant Pleural Mesothelioma	Initial Therapy: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until progression or unacceptable toxicity,-until disease progression or unacceptable toxicity for up to 2 years Subsequent Therapy: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease progression or unacceptable toxicity
* All treatments given for a maximum of 4 doses must be administered within 16 weeks of the first dose.	

LENGTH OF AUTHORIZATION

Coverage will be provided for six months and may be renewed (unless otherwise specified).

Renal Cell Carcinoma (RCC)/Cutaneous Melanoma (excluding adjuvant therapy)/Colorectal Cancer (CRC)/Small Bowel Adenocarcinoma (SBA)/Hepatocellular Carcinoma (HCC)/Uveal Melanoma/CNS metastases from Melanoma (combination therapy with nivolumab)

- Coverage will be provided for 12 weeks (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame) and may not be renewed *(Requests for Cutaneous Melanoma may be renewed if the patient meets the provisions for re-induction therapy).*

Non-Small Cell Lung Cancer (NSCLC)/Malignant Pleural Mesothelioma (excluding subsequent therapy)

- Coverage will be provided for up to a maximum of 2 years of therapy.

Cutaneous Melanoma (adjuvant therapy)

- Coverage for adjuvant treatment will be provided for six months and may be renewed for up to a maximum of 3 years of therapy

CNS metastases from Melanoma (single agent therapy)

- Coverage will be provided for 12 weeks initially (may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame). Coverage may be renewed in 6 month intervals thereafter.

Refer to **DOSAGE LIMITS** below

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.

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, the express terms of the health plan will govern.

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).

SOURCES

Lexi-Comp Online. (2020, March). AHFS DI. *Ipilimumab*. Retrieved October 5, 2020 from Lexi-Comp Online with AHFS.

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National Comprehensive Cancer Network. (2020). NCCN Drugs & Biologics Compendium™. *Ipilimumab*. Retrieved October 5, 2020 from the National Comprehensive Cancer Network.

U. S. Food and Drug Administration. (2020, October). Center for Drug Evaluation and Research. *Yervoy® (ipilimumab).* Retrieved November 11, 2020 from http://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125377s073lbl.pdf.

EFFECTIVE DATE 4/2/21

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