Yervoy® (ipilimumab)
(Intravenous)

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I. Length of Authorization Δ 1,5,6,8-12,17-19,20,24,27-29,31,33,39-42,44,46,49

Coverage will be provided for 6 months and may be renewed (unless otherwise specified).

- The following indications may be authorized up to a maximum of twelve (12) weeks of therapy and may NOT be renewed *(coverage may be extended to 16 weeks if 4 doses were not administered within the 12 week time frame)*:
  - Colorectal Cancer *(subsequent therapy/disease progression)*
  - CNS metastases from Melanoma *(combination therapy with nivolumab)*
  - Hepatocellular Carcinoma
  - Renal Cell Carcinoma
  - Cutaneous Melanoma *(first-line or subsequent therapy)*

    ***** *Requests for Cutaneous Melanoma may be renewed if the patient meets the provisions for re-induction therapy.*
  - Cutaneous Melanoma *(adjuvant therapy in combination with nivolumab)*
  - Uveal Melanoma
- The following indications may be renewed up to a maximum of two (2) years of therapy:
  - Biliary Tract Cancer
  - Bone Cancer
  - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer
  - Kaposi Sarcoma
  - Malignant Pleural Mesothelioma
  - Non-Small Cell Lung Cancer

Cutaneous Melanoma (single agent adjuvant treatment)

- Coverage will be provided for 6 months and may be renewed for up to a maximum of 3 years of maintenance therapy.

II. Dosing Limits

A. Quantity Limit (max daily dose) [NDC Unit]:

- Yervoy 200 mg/40 mL injection:
  - 5 vials per 84 days (initially up to 5 vials per 21 days x 4 doses)
- Yervoy 50 mg/10 mL injection:
  - 3 vials per 84 days (initially up to 3 vials per 21 days x 4 doses)

B. Max Units (per dose and over time) [HCPCS Unit]:

Indication	Billable Units (BU)	Per unit time (days)
HCC	350 BU	21 days x 4 doses
Cutaneous Melanoma, CNS metastases	Initial: 1150 BU	Initial: 21 days x 4 doses
	Followed by: 1150 BU	Followed by: 84 days
Uveal Melanoma	1150 BU	21 days x 4 doses
RCC	150 BU	21 days x 4 doses
Bone Cancer, CRC, Esophageal and Esophagogastric/Gastroesophageal Junction Cancer, MPM, NSCLC, Kaposi Sarcoma, Biliary Tract Cancer, Merkel Cell Carcinoma, Soft Tissue Sarcoma	150 BU	42 days

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

- Patient is at least 18 years of age, unless otherwise indicated; **AND**

Biliary Tract Cancers (Gallbladder Cancer or Intra-/Extra-Hepatic Cholangiocarcinoma) ‡ [2,46]

- Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used as subsequent treatment for progression on or after systemic treatment for unresectable, resected gross residual (R2), or metastatic disease; **AND**
- Used in combination with nivolumab

Bone Cancer ‡ [2,46]

- Patient has one of the following: Ewing sarcoma, Chondrosarcoma *(excluding mesenchymal chondrosarcoma)*, Osteosarcoma, or Chordoma; **AND**
- Patient has tumor mutation burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
- Used in combination with nivolumab; **AND**
- Patient has unresectable or metastatic disease that progressed following prior treatment; **AND**
- Patient has no satisfactory alternative treatment options

Central Nervous System (CNS) Cancer ‡ [2,4,8,10,11,27,82e]

- Used for the treatment of brain metastases in patients with BRAF non-specific melanoma; **AND**
- Used in combination with nivolumab or as a single agent; **AND**
- Used in one of the following treatment settings:
  - Used as initial treatment in patients with small asymptomatic brain metastases
  - Used for relapsed limited brain metastases with either stable systemic disease or reasonable systemic treatment options
  - Patient has recurrent limited brain metastases
  - Used for recurrent extensive brain metastases with stable systemic disease or reasonable systemic treatment options; **AND**

Ipilimumab as a single-agent ONLY:
• Use of ipilimumab as a single agent will be restricted to patients with a contraindication or intolerance to nivolumab

Colorectal Cancer (CRC) † ‡ [1,2,19,31,42,85e-87e,94e]

- Patient is at least 12 years of age; **AND**
- Patient has microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) disease; **AND**
- Patient has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.) [Δ]; **AND**
- Used in combination with nivolumab*; **AND**
  - Used as subsequent therapy; **AND**
    - Patient has metastatic, unresectable, or medically inoperable disease that progressed following treatment with a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based chemotherapy † ‡; **OR**
  - Used as primary treatment; **AND**
    - Used for one of the following:
      - Isolated pelvic/anastomotic recurrence of rectal cancer
      - Patient has metastatic, unresectable, or medically inoperable disease; **AND**

▪ Use of ipilimumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

** Single agent nivolumab should be used in patients who are not candidates for intensive therapy.*

Esophageal Cancer and Esophagogastric/Gastroesophageal Junction Cancers † [1,2,45,105e]

- Patient has esophageal squamous cell carcinoma (ESCC); **AND**

- Patient has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.) [Δ]; **AND**
- Used as first-line treatment in combination with nivolumab; **AND**
- Patient is not a surgical candidate or has unresectable advanced, recurrent, or metastatic disease; **AND**

- Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to one of the following:
  - Nivolumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin)
  - Pembrolizumab/(fluorouracil or capecitabine)/(cisplatin or oxaliplatin) *(CPS ≥10 only)*

Hepatocellular Carcinoma (HCC) † [1,2,30,30e,31e,33e,34e]

- Used in combination with nivolumab; **AND**
- Used as subsequent therapy for progressive disease; **AND**
- Patient progressed on or was intolerant to sorafenib or lenvatinib; **AND**
- Patient has Child-Pugh Class A hepatic impairment; **AND**
- Used for one of the following:
  - Patient has unresectable disease and is not a transplant candidate
  - Patient has liver-confined disease that is inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic-disease
  - Patient has metastatic disease or extensive liver tumor burden; **AND**

- Use of ipilimumab will be restricted to patients with a contraindication or intolerance to one of the following:
  - Regorafenib
  - Cabozantinib
  - Ramucirumab *(patients with AFP ≥ 400 ng/mL)*

Kaposi Sarcoma ‡ [2,47]

- Used in combination with nivolumab as subsequent therapy; **AND**
- Patient has classic disease; **AND**
- Used for relapsed/refractory advanced cutaneous, oral, visceral, or nodal disease; **AND**
- Disease has progressed on or not responded to first-line therapy; **AND**
- Disease has progressed on alternate first-line therapy; **AND**

<u>Cutaneous disease ONLY:</u>

- Use of ipilimumab in combination with nivolumab will be restricted to patients with a contraindication or intolerance to pembrolizumab

Renal Cell Carcinoma (RCC) † ‡ [1,2,18]

- Used in combination with nivolumab for clear cell histology; **AND**
  - Used as first-line therapy in patients with poor or intermediate risk advanced, relapsed, or stage IV disease; **OR**
  - Used as first-line therapy in patients with favorable risk relapsed or stage IV disease

Malignant Pleural Mesothelioma (MPM) † ‡ Φ [1,2,5,25,26,34,37]

- Used in combination with nivolumab; **AND**
  - Used as subsequent therapy (if chemotherapy was administered first-line); **AND**
    - Patient previously received platinum-containing chemotherapy; **OR**
  - Used as first-line therapy in patients with medically inoperable or unresectable disease

Cutaneous Melanoma † ‡ Φ [1,2,6,17,43,5e,8e,11e,13e,21e-23e,99e,100e]

- Used as first-line therapy for unresectable or metastatic* disease †; **AND**
  - Patient is at least 12 years of age; **AND**
  - Used as a single agent or in combination with nivolumab; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
  - Used after disease progression, intolerance, and/or projected risk of progression with BRAF-targeted therapy (e.g., dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib, etc.); **AND**
    - Used as a single agent in patients at least 12 years of age if not previously used alone or in combination with anti-PD-1 therapy †; **AND**

      > ➢ Patient must demonstrate an inadequate response to one of the following, unless there is a contraindication or intolerance, prior to approval of ipilimumab:
      > – Pembrolizumab (patients ≥ 18 years of age)
      > – Nivolumab; **OR**

    - Used in combination with nivolumab in patients at least 12 years of age if not previously used or for patients who progress on single agent anti-PD-1 therapy †; **OR**
    - Used in combination with pembrolizumab if not previously used alone or in combination with anti-PD-1 therapy for patients who progress on single agent anti-PD-1 therapy; **OR**
  - Used as re-induction therapy in patients who experienced disease control *(i.e., complete or partial response or stable disease)* and no residual toxicity from prior

use, but subsequently have disease progression/relapse > 3 months after treatment discontinuation; **AND**

- Used as a single agent; **AND**
- Patient has completed initial induction ipilimumab therapy (i.e., completion of 4 cycles within a 16 week period); **OR**

- Used as adjuvant treatment; **AND**
  - Used as a single agent; **AND**
    - Patient has stage III disease with pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †; **AND**

    - Use of ipilimumab for adjuvant therapy will be restricted to patients with a contraindication or intolerance to pembrolizumab or nivolumab; **OR**

  - Used in combination with nivolumab; **AND**
    - Patient has oligometastatic disease and no evidence of disease following metastasis-directed therapy (i.e., complete resection, stereotactic ablative therapy or T-VEC/intralesional therapy) or systemic therapy followed by resection

**Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, as well as unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.*

Uveal Melanoma ‡ [2,20-23,32]

- Patient has metastatic or unresectable disease; **AND**
  - Used as a single agent; **OR**
  - Used in combination with nivolumab as first-line therapy

Merkel Cell Carcinoma ‡ [2,50,51]

- Used for M1 disseminated disease; **AND**
- Used in combination with nivolumab; **AND**
- Patient progressed on anti-PD-L1 or anti-PD-1 therapy OR anti-PD-L1 or anti-PD-1 therapy is contraindicated

Non-Small Cell Lung Cancer (NSCLC) † ‡ [1,2,12,16,24,36,35e-37e,43e,50e,89e,110e]

- 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; **AND**
  - Used as first-line therapy; **AND**
    - Used for one of the following:

- Patients with a performance status (PS) 0-1 who have tumors that are negative for actionable molecular biomarkers** and PD-L1 <1%
- Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2)
- PD-L1 expression positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test❖, that are tumors that are negative for actionable molecular biomarkers**; **AND**

▪ Used in combination with one of the following:
- Nivolumab
- Nivolumab and platinum-doublet chemotherapy (e.g., pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology, or paclitaxel and carboplatin for squamous cell histology, etc.); **AND**

PD-L1 expression ≥50%:

▪ Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to cemiplimab; **OR**

PD-L1 <50% or EGFR exon 20, KRAS G12C, BRAF V600E, NTRK1/2/3 gene fusion, MET exon-14 skipping, RET rearrangement, or ERBB2 (HER2) mutation positive tumors:

Squamous NSCLC:

▪ Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to one of the following:
  - Pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel***)
  - Cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

****Albumin-bound paclitaxel may be used in place of paclitaxel in patients who meet the taxane-hypersensitivity criteria in Paclitaxel Albumin-Bound-E.*

Nonsquamous NSCLC:

▪ Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to one of the following:
  - Pembrolizumab/(carboplatin or cisplatin)/pemetrexed
  - Cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

- Used as subsequent therapy; **AND**

- Used for one of the following:
  - Patients with a PS 0-1 who are positive for one of the following molecular mutations and have received prior targeted therapy§: EGFR exon 19 deletion or exon 21 L858R tumors, EGFR S768I, L861Q, and/or G719X, ALK rearrangement, or ROS1 rearrangement
  - Patients with a PS 0-1 who are positive for one of the following molecular biomarkers: BRAF V600E, NTRK1/2/3 gene fusion, MET exon 14 skipping, or RET rearrangement; **AND**
- Used in combination with one of the following:
  - Nivolumab
  - Nivolumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
  - Nivolumab, paclitaxel, and carboplatin for squamous cell histology; **AND**

<u>EGFR T790M mutation-positive disease previously treated with erlotinib, afatinib, gefitinib, or dacomitinib ONLY:</u>

- Patient must demonstrate an inadequate response to osimertinib, unless there is a contraindication or intolerance, prior to approval of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy); **AND**

Squamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to one of the following
  - Pembrolizumab/carboplatin/(paclitaxel or albumin-bound paclitaxel***)
  - Cemiplimab/paclitaxel/(carboplatin or cisplatin); **OR**

****Albumin-bound paclitaxel may be used in place of paclitaxel in patients who meet the taxane-hypersensitivity criteria in Paclitaxel Albumin-Bound-E.*

Nonsquamous NSCLC:

- Use of ipilimumab in combination with nivolumab (with or without platinum-doublet chemotherapy) will be restricted to patients with a contraindication or intolerance to one of the following:
  - Pembrolizumab/(carboplatin or cisplatin)/pemetrexed
  - Cemiplimab/(paclitaxel or pemetrexed)/(carboplatin or cisplatin); **OR**

- Used as continuation maintenance therapy in combination with nivolumab; **AND**

- Patient has achieved a response or stable disease following first-line therapy with nivolumab and ipilimumab with or without chemotherapy

*** Note: Actionable molecular genomic biomarkers include EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET exon 14 skipping mutation, RET rearrangement, and ERBB2 (HER2). If there is insufficient tissue to allow testing for all of EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), 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.*

Soft Tissue Sarcoma ‡ [2,46,52]

- Extremity/Body Wall, Head/Neck or Retroperitoneal/Intra-Abdominal
  - Used in combination with nivolumab; **AND**
  - Used as subsequent therapy; **AND**
  - Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
  - Patient has no satisfactory alternative treatment options; **OR**
- Pleomorphic Rhabdomyosarcoma
  - Used in combination with nivolumab; **AND**
  - Used as subsequent therapy; **AND**
  - Patient has tumor mutational burden-high (TMB-H) [≥ 10 mutations/megabase (mut/Mb)] disease as determined by an FDA-approved or CLIA-compliant test❖; **AND**
  - Patient has no satisfactory alternative treatment options

Preferred therapies and recommendations are determined by review of clinical evidence. NCCN category of recommendation is taken into account as a component of this review. Regimens deemed equally efficacious (i.e., those having the same NCCN categorization) are considered to be therapeutically equivalent.

❖ *If confirmed using an FDA approved assay – http://www.fda.gov/CompanionDiagnostics*

† FDA Approved Indication(s); ‡ Compendia Recommended Indication; Φ Orphan Drug

§ Genomic Aberration/Mutational Driver Targeted Therapies (Note: *not all inclusive, refer to guidelines for appropriate use*)				
Sensitizing *EGFR* mutation-positive tumors	*ALK* rearrangement-positive tumors	*ROS1* rearrangement-positive tumors	*BRAF* V600E-mutation positive tumors	*NTRK1/2/3* gene fusion positive tumors
– Afatinib – Erlotinib – Dacomitinib – Gefitinib – Osimertinib	– Alectinib – Brigatinib – Ceritinib – Crizotinib – Lorlatinib	– Ceritinib – Crizotinib – Entrectinib – Lorlatinib	– Dabrafenib ± trametinib – Vemurafenib	– Larotrectinib – Entrectinib

– Amivantamab *(exon-20 insertion)* – Mobocertinib *(exon-20 insertion)*				
PD-L1 tumor expression ≥ 1%	*MET* exon-14 skipping mutations	*RET* rearrangement-positive tumors	*KRAS G12C* mutation positive tumors	*ERBB2 (HER2)* mutation positive tumors
– Pembrolizumab – Atezolizumab – Nivolumab + ipilimumab – Cemiplimab – Tremelimumab + durvalumab	– Capmatinib – Crizotinib – Tepotinib	– Selpercatinib – Cabozantinib – Pralsetinib	– Sotorasib – Adagrasib	– Fam-trastuzumab deruxtecan-nxki – Ado-trastuzumab emtansine

IV. Renewal Criteria Δ 1,2,6,9-12,17-29,39-41,46,49

Coverage may be renewed based upon the following criteria:

- Patient continues to meet the universal and other indication-specific relevant criteria such as concomitant therapy requirements (not including prerequisite therapy), performance status, etc. identified in section III; **AND**
- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include: immune-mediated reactions (e.g., colitis, hepatitis, dermatitis/rash, pneumonitis, nephritis/renal dysfunction, endocrinopathies, etc.), severe infusion reactions, complications of allogeneic hematopoietic stem cell transplantation (HSCT), etc.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Coverage may NOT be renewed for the following indications:
  - Colorectal Cancer *(subsequent therapy/disease progression)*
  - CNS metastases from Melanoma *(combination therapy with nivolumab)*
  - Hepatocellular Carcinoma
  - Renal Cell Carcinoma
  - Cutaneous Melanoma *(first-line or subsequent therapy)*

    ***** *Requests for Cutaneous Melanoma may be renewed if the patient meets the provisions for re-induction therapy (see below).*
  - Cutaneous Melanoma *(adjuvant therapy in combination with nivolumab)*
  - Uveal Melanoma
- For the following indications, patient has not exceeded a maximum of two (2) years of therapy:
  - Biliary Tract Cancer
  - Bone Cancer
  - Esophageal and Esophagogastric/Gastroesophageal Junction Cancer
  - Kaposi Sarcoma

– Malignant Pleural Mesothelioma
– Non-Small Cell Lung Cancer

Cutaneous Melanoma (re-induction therapy) ‡

- *Refer to Section III for criteria (see Cutaneous Melanoma – Used for retreatment of disease as re-induction)*

Cutaneous Melanoma (single agent adjuvant treatment – maintenance therapy)

- Patient has not exceeded a maximum of three (3) years of therapy

Non-Small Cell Lung Cancer (continuation maintenance therapy)

- *Refer to Section III for criteria*

Δ Notes:

- Patients responding to therapy who relapse ≥ 6 months after discontinuation due to duration (i.e., receipt of 24 months of PD-directed therapy) are eligible to re-initiate checkpoint inhibitor therapy.
- Patients who complete adjuvant therapy and progress ≥ 6 months after discontinuation are eligible to re-initiate checkpoint inhibitor therapy for metastatic disease.
- Patients whose tumors, upon re-biopsy, demonstrate a change in actionable mutation (e.g., MSS initial biopsy; MSI-H subsequent biopsy) may be eligible to re-initiate checkpoint inhibitor therapy and will be evaluated on a case-by-case basis.

V. Dosage/Administration Δ [1,5,6,8-12,17-29,31,33,34,38-42,44,46,49-52]

Indication	Dose
Renal Cell Carcinoma (RCC)	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Biliary Tract Cancers	In combination with nivolumab: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity for up to 24 months (2 years)
Bone Cancer	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity for up to 2 years
CNS metastases from Melanoma	Single agent: o Initial: Administer 10 mg/kg intravenously every 3 weeks for 4 doses o Subsequent (starting at week 24): Administer 10 mg/kg intravenously every 12 weeks until disease progression or unacceptable toxicity In combination with nivolumab: o Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)

Colorectal Cancer (CRC)	Primary/initial treatment o Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks), until disease progression or unacceptable toxicity Subsequent therapy/disease progression o Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Esophageal and Esophagogastric/ Gastroesophageal Junction Cancer	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 or 3 weeks) until disease progression or unacceptable toxicity for up to 2 years
Hepatocellular Carcinoma (HCC)	Administer 3 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Kaposi Sarcoma	In combination with nivolumab: Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 2 weeks) until disease progression or unacceptable toxicity for up to 24 months (2 years)
Malignant Pleural Mesothelioma (MPM)	Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 3 weeks) until disease progression or unacceptable toxicity for up to 2 years
Cutaneous Melanoma *(excluding adjuvant therapy)*	Single agent or in combination with nivolumab: o Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses (when given in combination with nivolumab, follow with nivolumab monotherapy) In combination with pembrolizumab as subsequent therapy: o Administer 1 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given in combination with pembrolizumab, then follow with pembrolizumab monotherapy)
Cutaneous Melanoma (adjuvant therapy)	Single agent o Initial: Administer 10 mg/kg intravenously every 3 weeks for up to a maximum of 4 doses o Maintenance: Administer 10 mg/kg intravenously every 12 weeks for up to 3 years In combination with nivolumab o Administer 3 mg/kg intravenously every 3 weeks for a maximum of 4 doses (given in combination with nivolumab)
Uveal Melanoma	Single agent: o Administer 3 mg/kg or 10mg/kg intravenously every 3 weeks for 4 doses In combination with nivolumab: o Administer 3 mg/kg intravenously every 3 weeks for 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Merkel Cell Carcinoma	In combination with nivolumab Administer 1 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity

Non-Small Cell Lung Cancer (NSCLC)	In combination with nivolumab: o Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 3 weeks), until disease progression or unacceptable toxicity for up to 2 years In combination with nivolumab and platinum-doublet chemotherapy: o Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab every 3 weeks and 2 cycles of histology-based platinum-doublet chemotherapy every 3 weeks), until disease progression or unacceptable toxicity for up to 2 years
Soft Tissue Sarcoma	In combination with nivolumab: Administer 1 mg/kg intravenously every 2 weeks 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.*	

VI. Billing Code/Availability Information

HCPCS Code:

- J9228 – Injection, ipilimumab, 1 mg; 1 billable unit = 1 mg

NDC(s):

- Yervoy 50 mg/10 mL injection (single-dose vial): 00003-2327-xx
- Yervoy 200 mg/40 mL injection (single-dose vial): 00003-2328-xx

VII. References (STANDARD)

1. Yervoy [package insert]. Princeton, NJ; Bristol Meyers Squib; February 2023. Accessed June 2023.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ipilimumab. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed June 2023.
3. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Small Cell Lung Cancer. Version 3.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed June 2023.
4. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Central Nervous System Cancers. Version 1.2023. National Comprehensive

Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed June 2023.

5. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Malignant Pleural Mesothelioma. Version 1.2023. National Comprehensive Cancer Network, 2023. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc. To view the most recent and complete version of the Guidelines, go online to NCCN.org. Accessed June 2023.
6. 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):711-23.
7. Wilgenhof S, Du Four S, Vandenbroucke F, et al. Single-center experience with ipilimumab in an expanded access program for patients with pretreated advanced melanoma. J Immunother. 2013 Apr; 36(3):215-22.
8. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol. 2012 May; 13(5):459-65.
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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C15.3	Malignant neoplasm of upper third of esophagus
C15.4	Malignant neoplasm of middle third of esophagus
C15.5	Malignant neoplasm of lower third of esophagus
C15.8	Malignant neoplasm of overlapping sites of esophagus
C15.9	Malignant neoplasm of esophagus, unspecified
C16.0	Malignant neoplasm of cardia
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.8	Malignant neoplasm of overlapping sites of small intestine
C17.9	Malignant neoplasm of small intestine, unspecified
C18.0	Malignant neoplasm of cecum
C18.1	Malignant neoplasm of appendix
C18.2	Malignant neoplasm of ascending colon
C18.3	Malignant neoplasm of hepatic flexure
C18.4	Malignant neoplasm of transverse colon

ICD-10	ICD-10 Description
C18.5	Malignant neoplasm of splenic flexure
C18.6	Malignant neoplasm of descending colon
C18.7	Malignant neoplasm of sigmoid colon
C18.8	Malignant neoplasm of overlapping sites of colon
C18.9	Malignant neoplasm of colon, unspecified
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C22.0	Liver cell carcinoma
C22.1	Intrahepatic bile duct carcinoma
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.8	Malignant neoplasm of overlapping sites of biliary tract
C24.9	Malignant neoplasm of biliary tract, unspecified
C33	Malignant neoplasm of trachea
C34.00	Malignant neoplasm of unspecified main bronchus
C34.01	Malignant neoplasm of right main bronchus
C34.02	Malignant neoplasm of left main bronchus
C34.10	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.11	Malignant neoplasm of upper lobe, right bronchus or lung
C34.12	Malignant neoplasm of upper lobe, left bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.31	Malignant neoplasm of lower lobe, right bronchus or lung
C34.32	Malignant neoplasm of lower lobe, left bronchus or lung
C34.80	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.81	Malignant neoplasm of overlapping sites of right bronchus and lung
C34.82	Malignant neoplasm of overlapping sites of left bronchus and lung
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C34.91	Malignant neoplasm of unspecified part of right bronchus or lung
C34.92	Malignant neoplasm of unspecified part of left bronchus or lung
C40.00	Malignant neoplasm of scapula and long bones of unspecified upper limb
C40.01	Malignant neoplasm of scapula and long bones of right upper limb
C40.02	Malignant neoplasm of scapula and long bones of left upper limb
C40.10	Malignant neoplasm of short bones of unspecified upper limb
C40.11	Malignant neoplasm of short bones of right upper limb

ICD-10	ICD-10 Description
C40.12	Malignant neoplasm of short bones of left upper limb
C40.20	Malignant neoplasm of long bones of unspecified lower limb
C40.21	Malignant neoplasm of long bones of right lower limb
C40.22	Malignant neoplasm of long bones of left lower limb
C40.30	Malignant neoplasm of short bones of unspecified lower limb
C40.31	Malignant neoplasm of short bones of right lower limb
C40.32	Malignant neoplasm of short bones of left lower limb
C40.80	Malignant neoplasm of overlapping sites of bone and articular cartilage of unspecified limb
C40.81	Malignant neoplasm of overlapping sites of bone and articular cartilage of right limb
C40.82	Malignant neoplasm of overlapping sites of bone and articular cartilage of left limb
C40.90	Malignant neoplasm of unspecified bones and articular cartilage of unspecified limb
C40.91	Malignant neoplasm of unspecified bones and articular cartilage of right limb
C40.92	Malignant neoplasm of unspecified bones and articular cartilage of left limb
C41.0	Malignant neoplasm of bones of skull and face
C41.1	Malignant neoplasm of mandible
C41.2	Malignant neoplasm of vertebral column
C41.3	Malignant neoplasm of ribs, sternum and clavicle
C41.4	Malignant neoplasm of pelvic bones, sacrum and coccyx
C41.9	Malignant neoplasm of bone and articular cartilage, unspecified
C43.0	Malignant melanoma of lip
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20	Malignant melanoma of unspecified ear and external auricular canal
C43.21	Malignant melanoma of right ear and external auricular canal
C43.22	Malignant melanoma of left ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60	Malignant melanoma of unspecified upper limb, including shoulder
C43.61	Malignant melanoma of right upper limb, including shoulder
C43.62	Malignant melanoma of left upper limb, including shoulder
C43.70	Malignant melanoma of unspecified lower limb, including hip

ICD-10	ICD-10 Description
C43.71	Malignant melanoma of right lower limb, including hip
C43.72	Malignant melanoma of left lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified
C45.0	Mesothelioma of pleura
C4A.0	Merkel cell carcinoma of lip
C4A.10	Merkel cell carcinoma of eyelid, including canthus
C4A.111	Merkel cell carcinoma of right upper eyelid, including canthus
C4A.112	Merkel cell carcinoma of right lower eyelid, including canthus
C4A.121	Merkel cell carcinoma of left upper eyelid, including canthus
C4A.122	Merkel cell carcinoma of left lower eyelid, including canthus
C4A.20	Merkel cell carcinoma of unspecified ear and external auricular canal
C4A.21	Merkel cell carcinoma of right ear and external auricular canal
C4A.22	Merkel cell carcinoma of left ear and external auricular canal
C4A.30	Merkel cell carcinoma of unspecified part of face
C4A.31	Merkel cell carcinoma of nose
C4A.39	Merkel cell carcinoma of other parts of face
C4A.4	Merkel cell carcinoma of scalp and neck
C4A.51	Merkel cell carcinoma of anal skin
C4A.52	Merkel cell carcinoma of skin of breast
C4A.59	Merkel cell carcinoma of other part of trunk
C4A.60	Merkel cell carcinoma of unspecified upper limb, including shoulder
C4A.61	Merkel cell carcinoma of right upper limb, including shoulder
C4A.62	Merkel cell carcinoma of left upper limb, including shoulder
C4A.70	Merkel cell carcinoma of unspecified lower limb, including hip
C4A.71	Merkel cell carcinoma of right lower limb, including hip
C4A.72	Merkel cell carcinoma of left lower limb, including hip
C4A.8	Merkel cell carcinoma of overlapping sites
C4A.9	Merkel cell carcinoma, unspecified
C46.0	Kaposi's sarcoma of skin
C46.1	Kaposi's sarcoma of soft tissue
C46.2	Kaposi's sarcoma of palate
C46.3	Kaposi's sarcoma of lymph nodes
C46.4	Kaposi's sarcoma of gastrointestinal sites
C46.50	Kaposi's sarcoma of unspecified lung
C46.51	Kaposi's sarcoma of right lung
C46.52	Kaposi's sarcoma of left lung
C46.7	Kaposi's sarcoma of other sites

ICD-10	ICD-10 Description
C46.9	Kaposi's sarcoma, unspecified
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck
C47.10	Malignant neoplasm of peripheral nerves of unspecified upper limb, including shoulder
C47.11	Malignant neoplasm of peripheral nerves of right upper limb, including shoulder
C47.12	Malignant neoplasm of peripheral nerves of left upper limb, including shoulder
C47.20	Malignant neoplasm of peripheral nerves of unspecified lower limb, including hip
C47.21	Malignant neoplasm of peripheral nerves of right lower limb, including hip
C47.22	Malignant neoplasm of peripheral nerves of left lower limb, including hip
C47.3	Malignant neoplasm of peripheral nerves of thorax
C47.4	Malignant neoplasm of peripheral nerves of abdomen
C47.5	Malignant neoplasm of peripheral nerves of pelvis
C47.6	Malignant neoplasm of peripheral nerves of trunk, unspecified
C47.8	Malignant neoplasm of overlapping sites of peripheral nerves and autonomic nervous system
C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system, unspecified
C48.0	Malignant neoplasm of retroperitoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C49.0	Malignant neoplasm of connective and soft tissue of head, face and neck
C49.10	Malignant neoplasm of connective and soft tissue of unspecified upper limb, including
C49.11	Malignant neoplasm of connective and soft tissue of right upper limb, including shoulder
C49.12	Malignant neoplasm of connective and soft tissue of left upper limb, including shoulder
C49.20	Malignant neoplasm of connective and soft tissue of unspecified lower limb, including hip
C49.21	Malignant neoplasm of connective and soft tissue of right lower limb, including hip
C49.22	Malignant neoplasm of connective and soft tissue of left lower limb, including hip
C49.3	Malignant neoplasm of connective and soft tissue of thorax
C49.4	Malignant neoplasm of connective and soft tissue of abdomen
C49.5	Malignant neoplasm of connective and soft tissue of pelvis
C49.6	Malignant neoplasm of connective and soft tissue of trunk, unspecified
C49.8	Malignant neoplasm of overlapping sites of connective and soft tissue
C49.9	Malignant neoplasm of connective and soft tissue, unspecified
C64.1	Malignant neoplasm of right kidney, except renal pelvis
C64.2	Malignant neoplasm of left kidney, except renal pelvis
C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1	Malignant neoplasm of right renal pelvis
C65.2	Malignant neoplasm of left renal pelvis
C65.9	Malignant neoplasm of unspecified renal pelvis
C69.30	Malignant neoplasm of unspecified choroid

ICD-10	ICD-10 Description
C69.31	Malignant neoplasm of right choroid
C69.32	Malignant neoplasm of left choroid
C69.40	Malignant neoplasm of unspecified ciliary body
C69.41	Malignant neoplasm of right ciliary body
C69.42	Malignant neoplasm of left ciliary body
C69.60	Malignant neoplasm of unspecified orbit
C69.61	Malignant neoplasm of right orbit
C69.62	Malignant neoplasm of left orbit
C7B.1	Secondary Merkel cell carcinoma
C72.0	Malignant neoplasm of spinal cord
C72.1	Malignant neoplasm of cauda equina
C78.00	Secondary malignant neoplasm of unspecified lung
C78.01	Secondary malignant neoplasm of right lung
C78.02	Secondary malignant neoplasm of left lung
C78.6	Secondary malignant neoplasm of retroperitoneum and peritoneum
C78.7	Secondary malignant neoplasm of liver and intrahepatic bile duct
C79.31	Secondary malignant neoplasm of brain
D37.8	Neoplasm of uncertain behavior of other specified digestive organs
D37.9	Neoplasm of uncertain behavior of digestive organ, unspecified
Z85.00	Personal history of malignant neoplasm of unspecified digestive organ
Z85.01	Personal history of malignant neoplasm of esophagus
Z85.068	Personal history of other malignant neoplasm of small intestine
Z85.118	Personal history of other malignant neoplasm of bronchus and lung
Z85.820	Personal history of malignant melanoma of skin
Z85.821	Personal history of Merkel cell carcinoma
Z85.830	Personal history of malignant neoplasm of bone
Z85.831	Personal history of malignant neoplasm of soft tissue

Appendix 2 – Centers for Medicare and Medicaid Services (CMS)

Medicare coverage for outpatient (Part B) drugs is outlined in the Medicare Benefit Policy Manual (Pub. 100-2), Chapter 15, §50 Drugs and Biologicals. In addition, National Coverage Determination (NCD), Local Coverage Determinations (LCDs), and Local Coverage Articles (LCAs) may exist and compliance with these policies is required where applicable. They can be found at: https://www.cms.gov/medicare-coverage-database/search.aspx. Additional indications may be covered at the discretion of the health plan.

Medicare Part B Covered Diagnosis Codes (applicable to existing NCD/LCD/LCA): N/A

Medicare Part B Administrative Contractor (MAC) Jurisdictions		
Jurisdiction	**Applicable State/US Territory**	**Contractor**
E (1)	CA, HI, NV, AS, GU, CNMI	Noridian Healthcare Solutions, LLC
F (2 & 3)	AK, WA, OR, ID, ND, SD, MT, WY, UT, AZ	Noridian Healthcare Solutions, LLC
5	KS, NE, IA, MO	Wisconsin Physicians Service Insurance Corp (WPS)
6	MN, WI, IL	National Government Services, Inc. (NGS)
H (4 & 7)	LA, AR, MS, TX, OK, CO, NM	Novitas Solutions, Inc.
8	MI, IN	Wisconsin Physicians Service Insurance Corp (WPS)
N (9)	FL, PR, VI	First Coast Service Options, Inc.
J (10)	TN, GA, AL	Palmetto GBA, LLC
M (11)	NC, SC, WV, VA (excluding below)	Palmetto GBA, LLC
L (12)	DE, MD, PA, NJ, DC (includes Arlington & Fairfax counties and the city of Alexandria in VA)	Novitas Solutions, Inc.
K (13 & 14)	NY, CT, MA, RI, VT, ME, NH	National Government Services, Inc. (NGS)
15	KY, OH	CGS Administrators, LLC