Yervoy® (ipilimumab)
(Intravenous)

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I. 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/Hepatocellular Carcinoma (HCC)/Uveal Melanoma/CNS metastases from Melanoma (combination therapy with nivolumab) [1,6,9,10,11,17-19,20,27,29,33]

- 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) [1,12,24]

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

Cutaneous Melanoma (adjuvant therapy) [1,6,17]

- 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) [8,28]

- 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.

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)
Cutaneous Melanoma (excluding adjuvant therapy)	350 BU	21 days x 4 doses
Cutaneous Melanoma (adjuvant therapy), CNS metastases from melanoma	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
CRC, RCC, SBA	115 BU	21 days x 4 doses
MPM, NSCLC	115 BU	42 days
HCC	350 BU	21 days x 4 doses

III. Initial Approval Criteria [1]

Coverage is provided in the following conditions:

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

Cutaneous Melanoma † Φ [1,2,6,17]

- Used as first-line therapy for unresectable or metastatic disease in combination with nivolumab; **OR**
- Used for unresectable or metastatic disease previously treated with cytotoxic chemotherapy as a single agent in patients at least 12 years of age †; **OR**
- Used as subsequent therapy for unresectable or metastatic* disease; **AND**
    - 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**
        - Used as a single agent or in combination with nivolumab if checkpoint inhibitor immunotherapy was not previously used; **OR**
        - Used as a single agent or in combination with nivolumab for patients who progressed on single agent checkpoint inhibitor immunotherapy; **OR**
    - Used for retreatment of disease as re-induction as a single agent or in combination with nivolumab in patients 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**
        - Patient has completed initial induction (completion of 4 cycles within a 16 week period); **OR**
- Used as a single-agent for adjuvant therapy; **AND**
    - Patient has pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †; **OR**
    - Patient has previously received anti-PD-1 therapy (e.g., nivolumab or pembrolizumab); **AND**

- Patient has local satellite/in-transit recurrence and has no evidence of disease (NED) after complete excision ‡; **OR**
- Patient has undergone therapeutic lymph node dissection (TLND) and/or complete resection of nodal recurrence ‡; **OR**
- Patient 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 patients with limited resectable and unresectable disease, unresectable nodal recurrence, and disseminated (unresectable) distant metastatic disease*

Uveal Melanoma ‡ [2,20-23,32]

- Used as a single agent or in combination with nivolumab for distant metastatic disease

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 advanced, relapsed, or stage IV disease with poor or intermediate risk; **OR**
  - Used as first-line therapy in patients with relapsed or stage IV disease with favorable risk; **OR**
  - Used as subsequent therapy in patients with relapsed or stage IV disease

Non-Small Cell Lung Cancer (NSCLC) † [2,16,24]

- Patient 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; **OR**
- 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:
      - Used in patients 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 patients 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 patients with PS 0-2 for PD-L1 expression positive (PD-L1 ≥1%) tumors, as detected by an FDA or CLIA compliant test§§, that are EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET rearrangement negative**; **AND**
    - Used in combination with nivolumab; **OR**

- Used 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.); **OR**

- Used as subsequent therapy; **AND**
  - Used for one of the following:
    - Used in patients with PS 0-1 who have EGFR, ALK, or ROS1 positive tumors and have received prior targeted therapy**§**
    - Used in patients 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; **AND**
      - Used in combination with nivolumab; **OR**
      - Used in combination with nivolumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology; **OR**
      - Used in combination with nivolumab, paclitaxel and carboplatin for squamous cell histology

**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.*

Malignant Pleural Mesothelioma † ‡ [2,5,25,26,34,37]

- Used in combination with nivolumab; **AND**
  - Used as subsequent therapy; **OR**
  - Used as first-line therapy in patients with unresectable disease

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

- Used for the treatment of brain metastases in patients with melanoma; **AND**
- Used in combination with nivolumab or as a single agent; **AND**
  - Used as initial treatment in patients with small asymptomatic brain metastases; **OR**
  - Used for relapsed disease in patients with limited brain metastases and stable systemic disease or reasonable treatment options; **OR**
  - Patient has recurrent limited brain metastases; **OR**
  - Used for recurrent disease in patients with extensive brain metastases and stable systemic disease or reasonable systemic treatment options

Colorectal Cancer † [1,2,19,31]

- Patient is at least 12 years of age; **AND**
- Used in combination with nivolumab; **AND**

- Patient's disease is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
    - Patient has advanced or metastatic disease that has progressed following a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based regimen; **OR**
    - Used as primary treatment for unresectable metastatic disease after previous adjuvant therapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months

Small Bowel Adenocarcinoma ‡ [2,19,29]

- Patient has advanced or metastatic disease that is microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
- Used in combination with nivolumab in one of the following settings:
    - As subsequent therapy; **OR**
    - As initial therapy in patients with prior oxaliplatin exposure in the adjuvant setting or a contraindication

Hepatocellular Carcinoma (HCC) † [1,2,30]

- Patient has locally advanced, unresectable, inoperable, or metastatic disease; **AND**
- Used as subsequent therapy; **AND**
- Patient has Child-Pugh Class A disease; **AND**
- Used in combination with nivolumab; **AND**
- Patient has not previously received treatment with a checkpoint inhibitor (e.g., nivolumab, pembrolizumab, etc.)

§§ *If confirmed using an immunotherapy assay-http://www.fda.gov/CcompanionDiagnostics*

† 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 – Afatinib – Erlotinib – Dacomitinib – 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 – Selpercatinib – Cabozantinib – Vandetanib

IV. Renewal Criteria [1,2,6,9-12,17-29]

- Patient continues to meet 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. 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.; **AND**
- Disease response with treatment as defined by stabilization of disease or decrease in size of tumor or tumor spread; **AND**
- Coverage may <u>not</u> 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)

Cutaneous Melanoma Re-induction ‡

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

Cutaneous Melanoma Maintenance therapy (adjuvant treatment)

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

Non-Small Cell Lung Cancer (NSCLC)

- Patient has not exceeded a maximum of two (2) years of therapy

MPM (initial therapy)

- Patient has not exceeded a maximum of two (2) years of therapy

V. Dosage/Administration[1,6,8-12,17-29,33,34]

Indication	Dose
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 10mg/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, then follow with 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), Small Bowel Adenocarcinoma (SBA)	Administer 1 mg/kg intravenously every 3 weeks for a total of 4 doses (given in combination with nivolumab, then follow with nivolumab monotherapy)
Malignant Pleural Mesothelioma	Initial Therapy: – Administer 1 mg/kg intravenously every 6 weeks (given in combination with nivolumab) until disease 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.*	

VI. Billing Code/Availability Information

HCPCS Code:

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

NDC(s):

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

VII. References

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Appendix 1 – Covered Diagnosis Codes

ICD-10	ICD-10 Description
C17.0	Malignant neoplasm of duodenum
C17.1	Malignant neoplasm of jejunum
C17.2	Malignant neoplasm of ileum
C17.3	Meckel's diverticulum, malignant
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
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
C22.8	Malignant neoplasm of liver, primary, unspecified as to type
C22.9	Malignant neoplasm of liver, not specified as primary or secondary
C33	Malignant neoplasm of trachea

ICD-10	ICD-10 Description
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
C38.4	Malignant neoplasm of pleura
C43.0	Malignant melanoma of lip
C43.10	Malignant melanoma of unspecified eyelid, including canthus
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
C43.71	Malignant melanoma of right lower limb, including hip

ICD-10	ICD-10 Description
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
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
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
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
Z85.038	Personal history of other malignant neoplasm of large intestine
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

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: http://www.cms.gov/medicare-coverage-database/search/advanced-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):

Jurisdiction(s): J&M	**NCD/LCD/Article Document (s):** A56141
https://www.cms.gov/medicare-coverage-database/search/article-date-search.aspx?DocID=A56141&bc=gAAAAAAAAAAA	

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