



Yervoy™ (ipilimumab)

(Intravenous)

Document Number: IC-0148

Last Review Date: 06/03/2019

Date of Origin: 11/28/2011

Dates Reviewed: 12/2011, 03/2012, 06/2012, 09/2012, 12/2012, 05/2013, 06/2013, 09/2013, 12/2013, 03/2014, 06/2014, 09/2014, 12/2014, 03/2015, 05/2015, 08/2015, 10/2015, 11/2015, 02/2016, 05/2016, 08/2016, 11/2016, 01/2017, 05/2017, 08/2017, 11/2017, 02/2018, 05/2018, 08/2018, 12/2018, 03/2019, 06/2019

I. Length of Authorization

Small and Non-Small Cell Lung Cancer (SCLC/NSCLC)/Renal Cell Carcinoma (RCC)/Melanoma (unresectable or metastatic)/Colorectal Cancer (CRC)

- 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 (*unless the patient meets the provisions for metastatic or unresectable melanoma re-induction*).

Melanoma (maintenance adjuvant therapy)

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

Malignant Pleural Mesothelioma (MPM)

- Coverage will be provided for 6 months and may be renewed.

CNS metastases from Melanoma

- 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) [Pharmacy Benefit]:

- 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) [Medical Benefit]:

- **Unresectable or metastatic Melanoma**
 - 350 billable units per 21 days x 4 doses

- **Adjuvant treatment of Melanoma**
 - 1150 billable units per 21 days x 4 doses; then 1150 billable units per 84 days
- **CNS metastases from Melanoma**
 - Initial authorization: 1150 billable units per 21 days x 4 doses
 - Subsequent authorizations: 1150 billable units per 84 days
- **Colorectal Cancer (CRC)**
 - 115 billable units per 21 days x 4 doses
- **Renal Cell Carcinoma (RCC)**
 - 115 billable units per 21 days x 4 doses
- **Malignant Pleural Mesothelioma**
 - 115 billable units per 42 days
- **Small Cell Lung Cancer (SCLC)/Non-Small Cell Lung Cancer (NSCLC)**
 - 350 billable units per 21 days x 4 doses

III. Initial Approval Criteria

Coverage is provided in the following conditions:

- Patient is 18 years or older, unless otherwise indicated; **AND**

Melanoma †

- Patient's disease is unresectable or metastatic; **AND**
 - Used as a single agent in patients 12 years or older ‡; **OR**
 - Used in combination with nivolumab; **OR**
 - Used for retreatment of disease as re-induction **OR** subsequent to progression on single-agent checkpoint inhibitor therapy or maximum clinical benefit from BRAF-targeted therapy (*refer to Section IV for criteria*); **OR**
- Used as single-agent adjuvant treatment; **AND**
 - Patient has cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm and has undergone complete resection including total lymphadenectomy †; **OR**
 - Following complete lymph node dissection and/or complete resection of nodal recurrence and patient has previously received nivolumab or pembrolizumab ‡; **OR**
 - Following complete resection of distant metastatic disease and patient has previously received nivolumab or pembrolizumab ‡; **OR**
- Used as a single agent or in combination with nivolumab for unresectable or metastatic uveal melanoma ‡

Renal Cell Carcinoma (RCC) †

- Used as initial therapy in combination with nivolumab; **AND**
 - Patient has advanced or metastatic disease with intermediate or poor risk; **OR**

- Patient has relapsed or stage IV disease, predominantly clear cell histology, and favorable risk; **OR**
- Used as subsequent therapy in combination with nivolumab ‡; **AND**
 - Patient has relapsed or stage IV disease; **AND**
 - Patient has predominantly clear cell histology

Small Cell Lung Cancer (SCLC) ‡

- Used as subsequent therapy in combination with nivolumab; **AND**
- Patient has performance status of 0-2; **AND**
 - Used for primary progressive disease; **OR**
 - Used for relapse within 6 months of initial therapy following a complete or partial response or stable disease

Non-Small Cell Lung Cancer (NSCLC) ‡

- Used as first-line therapy in combination with nivolumab; **AND**
- Patient has metastatic disease with a high tumor mutational burden (TMB)* (i.e., ≥10 mutations per megabase)

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

Malignant Pleural Mesothelioma ‡

- Used in combination with nivolumab as subsequent therapy

Central nervous system cancers ‡

- Patient must have brain metastases from melanoma; **AND**
- Ipilimumab must have been active against the primary melanoma tumor; **AND**
 - Used as initial therapy in combination with nivolumab; **OR**
 - Used for recurrent disease as a single agent or in combination with nivolumab

Colorectal Cancer †

- Patient must be at least 12 years of age; **AND**
- Used in combination with nivolumab; **AND**
- Patient's disease must be microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR); **AND**
 - Patient has unresectable advanced or metastatic disease that has progressed following a fluoropyrimidine-, oxaliplatin-, and/or irinotecan-based regimen; **OR**
 - Used as primary treatment for metastatic disease after adjuvant therapy with a fluoropyrimidine and oxaliplatin regimen within the past 12 months

† FDA approved indication(s); ‡ Compendia recommended indication

IV. Renewal Criteria

- Patient continues to meet the criteria identified in section III; **AND**

- Absence of unacceptable toxicity from the drug. Examples of unacceptable toxicity include the following: immune-mediated reactions (e.g. enterocolitis, hepatitis, dermatitis, neuropathies, pneumonitis, nephritis/renal dysfunction, encephalitis, endocrinopathies like hypopituitarism, hypothyroidism, hypogonadism, or adrenal insufficiency, and ocular disease, etc); **AND**

Melanoma (metastatic or unresectable disease) ‡

- Patient has completed initial induction (completion of 4 cycles within a 16 week period); **AND**
 - Used as re-induction therapy as a single agent or in combination with nivolumab in patients who experienced disease control (i.e., complete or partial response or stable disease), but subsequently disease progression/relapse > 3 months after treatment discontinuation; **OR**
- Used as subsequent therapy in patients who experienced disease progression, in combination with nivolumab after monotherapy with an checkpoint-inhibitor or as a single-agent if a checkpoint-inhibitor was not previously used

Melanoma Maintenance therapy (adjuvant treatment)

- Tumor response/absence of recurrence; **AND**
- Length of therapy has not exceeded 3 years

CNS metastases from melanoma

- Initial renewal: Patient’s disease is clinically stable at week 24
- Subsequent renewals: Tumor response/absence of recurrence

Malignant Pleural Mesothelioma

- Tumor response with stabilization of disease or decrease in size of tumor or tumor spread.

Non-Small Cell Lung Cancer (NSCLC)/Small Cell Lung Cancer (SCLC)/Renal Cell Carcinoma (RCC)/Colorectal Cancer (CRC)

- Coverage may not be renewed.

V. Dosage/Administration

| Indication | Dose |
|---------------------------------------|--|
| Melanoma (unresectable or metastatic) | 3 mg/kg every 3 weeks for a maximum of 4 doses <i>* all treatment must be administered within 16 weeks of the first dose</i> |
| Melanoma (adjuvant) | 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years |
| CNS metastases from melanoma | <p><u>Single Agent</u></p> <ul style="list-style-type: none"> – <u>Initial</u>: 10 mg/kg every 3 weeks for 4 doses – <u>Subsequent</u>: 10 mg/kg every 12 weeks <p><u>Combination Therapy (with nivolumab)</u></p> <ul style="list-style-type: none"> – <u>Initial</u>: Ipilimumab 3 mg/kg and Nivolumab 1mg/kg every 3 weeks for 4 doses |

| | |
|---|---|
| | – <u>Subsequent</u> : Nivolumab 3 mg/kg every 2 weeks until disease progression or intolerance |
| Small Cell Lung Cancer (SCLC), Non-Small Cell Lung Cancer (NSCLC) | 3 mg/kg every 3 weeks for a total of 4 doses (given in combination with nivolumab followed by nivolumab monotherapy) * <i>all treatment must be administered within 16 weeks of the first dose</i> |
| Renal Cell Carcinoma (RCC) and Colorectal Cancer (CRC) | 1 mg/kg every 3 weeks for a total of 4 doses (given in combination with nivolumab followed by nivolumab monotherapy) |
| Malignant Pleural Mesothelioma | 1 mg/kg every 6 weeks until progression or unacceptable toxicity, given in combination with nivolumab |

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: 00003-2328-xx
- Yervoy 50 mg/10 mL injection: 0003-2327-xx

VII. References

1. Yervoy [package insert]. Princeton, NJ; Bristol Meyers Squib; May 2019. Accessed May 2019.
2. Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) ipilimumab. National Comprehensive Cancer Network, 2019. 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 May 2019.
3. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Small Cell Lung Cancer. National Comprehensive Cancer Network, Version 1.2019. 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 May 2019.
4. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Central Nervous System Cancers. National Comprehensive Cancer Network, Version 1.2019. 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 May 2019.

5. Referenced with permission from the NCCN Clinical Practice Guidelines (NCCN Guidelines®) Malignant Pleural Mesothelioma. National Comprehensive Cancer Network, Version 2.2019. 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 May 2019.
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9. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol.* 2016 Jul;17(7):883-895
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11. Long GV, Atkinson V, Menzies AM, et al. A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC). *Journal of Clinical Oncology* 35, no. 15_suppl (May 2017) 9508-9508.
12. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N Engl J Med* 2018; 378:2093-2104.

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 |
| C17.8 | 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 |

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| ICD-10 | ICD-10 Description |
|--------|--|
| 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 |
| 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 |
| C38.4 | Malignant neoplasm of pleura |
| C43.0 | Malignant melanoma of lip |
| C43.10 | Malignant melanoma of unspecified eyelid, including canthus |
| C43.11 | Malignant melanoma of right eyelid, including canthus |
| C43.12 | Malignant melanoma of left 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 |

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| ICD-10 | ICD-10 Description |
|--------|--|
| 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 |
| 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 |
| C69.90 | Malignant neoplasm of unspecified site of unspecified eye |
| C69.91 | Malignant neoplasm of unspecified site of right eye |
| C69.92 | Malignant neoplasm of unspecified site of left eye |
| 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 |
| C79.51 | Secondary malignant neoplasm of bone |
| C79.52 | Secondary malignant neoplasm of bone marrow |

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| ICD-10 | ICD-10 Description |
|---------|---|
| C7A.1 | Malignant poorly differentiated neuroendocrine tumors |
| C80.0 | Disseminated malignant neoplasm, unspecified |
| C80.1 | Malignant (primary) neoplasm, unspecified |
| 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 |
| Z85.528 | Personal history of other malignant neoplasm of kidney |
| 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) and Local Coverage Determinations (LCDs) 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): 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 |