

## **Clinical Policy: Ipilimumab (Yervoy)**

Reference Number: CP.PHAR.319

Effective Date: 04.17.18

Last Review Date: 08.18

Line of Business: Medicaid, HIM-Medical Benefit

[Coding Implications](#)

[Revision Log](#)

See [Important Reminder](#) at the end of this policy for important regulatory and legal information.

### **Description**

Ipilimumab (Yervoy<sup>®</sup>) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody.

### **FDA Approved Indication(s)**

Yervoy is indicated for:

- Treatment of unresectable or metastatic melanoma in adults and pediatric patients (12 years and older)
- Adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
- Treatment of patients with intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with nivolumab
- Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab

### **Policy/Criteria**

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation<sup>®</sup> that Yervoy is **medically necessary** when the following criteria are met:

#### **I. Initial Approval Criteria**

##### **A. Cutaneous Melanoma** (must meet all):

1. Diagnosis of cutaneous melanoma with pathologic involvement of regional lymph nodes;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  12 years;
4. Request meets one of the following (a or b):
  - a. Dose does not exceed 10 mg/kg;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**B. Unresectable or Metastatic Melanoma** (must meet all):

1. Diagnosis of one of the following (a or b):
  - a. Unresectable or metastatic melanoma;
  - b. Brain metastasis from melanoma as primary tumor;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  12 years;
4. Request meets one of the following (a or b):
  - a. Dose does not exceed 3 mg/kg per dose for a maximum of 4 doses over 16 weeks;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 16 weeks (maximum of 4 doses)**

**C. Renal Cell Carcinoma** (must meet all):

1. Diagnosis of renal cell carcinoma;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  12 years;
4. Prescribed in combination with Opdivo<sup>®</sup>;
5. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses.

**Approval duration: 16 weeks (maximum of 4 doses)**

**D. Colorectal Cancer** (must meet all):

1. Diagnosis of MSI-H or dMMR colorectal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  12 years;
4. Disease is unresectable or metastatic;
5. Prescribed in combination with Opdivo;
6. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses.

**Approval duration: 16 weeks (maximum of 4 doses)**

**E. Small Cell Lung Cancer (off-label)** (must meet all):

1. Diagnosis of small cell lung cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age  $\geq$  12 years;
4. Failure of a platinum-containing regimen (e.g. cisplatin, carboplatin), unless contraindicated or clinically significant adverse effects are experienced;  
*\*Prior authorization is (or may be) required for platinum-containing regimens*
5. Prescribed in combination with Opdivo;
6. Request meets one of the following (a or b):
  - a. Dose does not exceed 3 mg/kg per dose;
  - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 6 months**

**F. Other diagnoses/indications**

1. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

## II. Continued Therapy

### A. Unresectable or Metastatic Melanoma

1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial approval criteria, at a minimum of 3 months since initial treatment discontinuation.

**Approval duration: Not applicable**

### B. Renal Cell Carcinoma, Colorectal Cancer

1. Reauthorization beyond 16 weeks is not permitted. Members must meet the initial approval criteria.

**Approval duration: Not applicable**

### C. Cutaneous Melanoma (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy for cutaneous melanoma and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
  - a. New dose does not exceed 10 mg/kg per dose;
  - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months or up to a total duration of 3 years, whichever is less**

### D. Small Cell Lung Cancer (off-label) (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy for small cell lung cancer and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):
  - a. New dose does not exceed 3 mg/kg per dose;
  - b. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Approval duration: 12 months**

### E. Other diagnoses/indications (must meet 1 or 2):

1. Currently receiving medication via Centene benefit and documentation supports positive response to therapy.  
**Approval duration: Duration of request or 6 months (whichever is less);** or
2. Refer to the off-label use policy for the relevant line of business if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized): CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

- A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.PMN.53 for Medicaid or evidence of coverage documents.

**IV. Appendices/General Information**

*Appendix A: Abbreviation/Acronym Key*

- |  |  |
|--|--|
| CRC: colorectal cancer                   | dMMR: mismatch repair deficient        |
| CTLA-4: cytotoxic T-lymphocyte antigen 4 | FDA: Food and Drug Administration      |
|  | MSI-H: microsatellite instability-high |

*Appendix B: Therapeutic Alternatives*

*This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be a formulary agent and may require prior authorization.*

<b>Drug Name</b>	<b>Dosing Regimen</b>	<b>Dose Limit/ Maximum Dose</b>
Opdivo® (nivolumab)	<p><b>Renal cell carcinoma</b> Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks</p> <p><b>Small cell lung cancer</b> 1 mg/kg to 3 mg/kg IV every 2 weeks with or without ipilimumab</p> <p><b>MSI-H/dMMR CRC</b> 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for 4 doses, then nivolumab 240 mg IV as a single agent every 2 weeks until disease progression or unacceptable toxicity</p>	<p>RCC, SCLC: 480 mg/dose</p> <p>CRC: 240 mg/dose</p>
cisplatin- or carboplatin-containing regimen	<p><b>Small cell lung cancer</b> Varies</p>	Varies

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications*

- Bristol-Myers Squibb was released from the REMS program for Yervoy in March 2015.
- Black Box Warning: Immune-mediated adverse reactions
  - Yervoy can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy.

- The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of Yervoy.
- Permanently discontinue Yervoy and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.
  - Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotrophic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.
  - Yervoy should be permanently discontinued for severe or life-threatening:
    - Transaminase or total bilirubin elevation
    - Pneumonitis
    - Life-threatening serum creatinine elevation
    - Immune-mediated encephalitis

*Appendix D: General Information*

- NCCN lists Yervoy in combination with Opdivo with a category 2A recommendation for use in small cell lung cancer as subsequent systemic therapy for patients with:
  - Performance status 0-2 with relapse within 6 months following complete or partial response
  - Stable disease with initial treatment
  - Patients with primary progressive disease.

**V. Dosage and Administration**

Indication	Dosing Regimen	Maximum Dose
Cutaneous melanoma	10 mg/kg IV every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.	10 mg/kg/dose
Unresectable or metastatic melanoma or small cell lung cancer	3 mg/kg IV every 3 weeks for a total of 4 doses	3 mg/kg/dose
Advanced renal cell carcinoma	Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks	1 mg/kg/dose
Colorectal cancer	Nivolumab 3 mg/kg IV, followed by ipilimumab 1 mg/kg IV on the same day, every 3 weeks for a maximum of 4 doses, then nivolumab 240 mg IV every 2 weeks	1 mg/kg/dose

**VI. Product Availability**

Single-use vials: 50 mg/10 mL, 200 mg/40 mL

**VII. References**

1. Yervoy Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; July 2018. Available at: [https://packageinserts.bms.com/pi/pi\\_yervoy.pdf](https://packageinserts.bms.com/pi/pi_yervoy.pdf). Accessed July 16, 2018.
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3. Kidney cancer (Version 4.2018). In: National Comprehensive Cancer Network Guidelines. Available at [https://www.nccn.org/professionals/physician\\_gls/pdf/kidney.pdf](https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf). Accessed May 15, 2018.
4. Melanoma (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at [https://www.nccn.org/professionals/physician\\_gls/pdf/melanoma.pdf](https://www.nccn.org/professionals/physician_gls/pdf/melanoma.pdf). Accessed May 15, 2018.
5. Small cell lung cancer (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at [https://www.nccn.org/professionals/physician\\_gls/pdf/sclc.pdf](https://www.nccn.org/professionals/physician_gls/pdf/sclc.pdf). Accessed May 15, 2018.
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7. Rectal cancer (Version 2.2018). In: National Comprehensive Cancer Network Guidelines. Available at [https://www.nccn.org/professionals/physician\\_gls/pdf/rectal.pdf](https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf). Accessed April 16, 2018.

**Coding Implications**

Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPCS Codes	Description
J9228	Injection, ipilimumab, 1 mg

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Policy split from CP.PHAR.182 Excellus Oncology. Off-label NCCN recommended uses added.	01.17	03.17
Added age limit of $\geq 12$ years per package labeling. Added coverage criteria for small cell lung cancer. Previously the off-label diagnosis was covered, but without any coverage requirements. Added off-label NCCN recommended uses for malignant pleural mesothelioma and brain metastases from melanoma. For Continued Therapy, removed requirement to check for safety-related reasons to discontinue therapy, per the PA Policy for Safety Precautions.	08.29.17	11.17

Reviews, Revisions, and Approvals	Date	P&T Approval Date
Criteria added for new FDA indication: advanced renal cell carcinoma in combination with nivolumab; removed malignant pleural mesothelioma due to NCCN 2B recommendation status; added oncologist specialist requirement for all covered indications; summarized NCCN and FDA-approved uses for improved clarity; added up to a total tx duration of 3 years for cutaneous melanoma per PI; added failure of platinum-containing chemotx for SCLC per NCCN; allowed continuity of care for continued approval; clarified continued therapy language for unresectable or metastatic melanoma that reauthorization beyond 16 weeks is not permitted from reauthorization is not permitted; references reviewed and updated. Criteria added for new FDA indication: colorectal cancer in combination with nivolumab; references reviewed and updated.	07.24.18	08.18

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. “Health Plan” means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

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**Note:**

**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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