

Clinical Policy: Ipilimumab (Yervoy)

Reference Number: CP.PHAR.319

Effective Date: 04.17.18

Last Review Date: 08.20

Line of Business: Commercial, HIM, Medicaid

[Coding Implications](#)

[Revision Log](#)

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

Description

Ipilimumab (Yervoy[®]) 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*
- In combination with nivolumab, the treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib*
- In combination with nivolumab, for the first-line treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express programmed death-ligand 1 (PD-L1) $\geq 1\%$ as determined by an FDA-approved test, with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations
- In combination with nivolumab and 2 cycles of platinum-doublet chemotherapy, for the first-line treatment of adult patients with metastatic or recurrent NSCLC, with no EGFR or ALK genomic tumor aberrations

*This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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[®] 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 per kg;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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[®];*
**Prior authorization may be required for Opdivo*
5. Request meets one of the following (a or b):*
 - a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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. Request meets one of the following (a or b):*

- a. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
- b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 16 weeks (maximum of 4 doses)

E. Hepatocellular Carcinoma (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Member has previously received Nexavar[®];
**Prior authorization may be required for Nexavar*
5. Prescribed in combination with Opdivo;
**Prior authorization may be required for Opdivo*
6. Documentation of Child-Pugh Class A status;
7. Member has not had previous treatment with a checkpoint inhibitor (e.g., Opdivo, Keytruda[®], Tecentriq[®], Imfinzi[®]);
8. Request meets one of the following (a or b):*
 - a. Dose does not exceed 3 mg/kg IV every 3 weeks for a maximum of 4 doses;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 16 weeks (maximum of 4 doses)

F. Non-Small Cell Lung Cancer (must meet all):

1. Diagnosis of recurrent, advanced or metastatic NSCLC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 18 years;
4. Prescribed in combination with Opdivo;
**Prior authorization may be required for Opdivo*
5. Member has not previously progressed on a PD-1/PD-L1 inhibitor (e.g., Opdivo, Keytruda, Tecentriq, Imfinzi);
6. Request meets one of the following (a or b):
 - a. Disease mutation status is unknown or negative for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET, and member has not received no prior systemic therapy for advanced disease;
 - b. Disease mutation status is positive for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping or RET, and member has received mutation-specific treatment;
7. Request meets one of the following (a or b):
 - a. Member has PD-L1 tumor expression of \geq 1%;
 - b. Yervoy is being used in combination with Opdivo and platinum-doublet chemotherapy (*see Appendix B*);
8. Request meets one of the following (a or b):*
 - a. Dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
 - b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

9. Approval duration: 6 months

G. NCCN Compendium Indications (off-label) (must meet all):

1. Diagnosis of one of the following (a, b, c, or d):
 - a. Small cell lung cancer and prescribed in combination with Opdivo;*
 - b. Malignant pleural mesothelioma and prescribed in combination with Opdivo;*
 - c. MSI-H or dMMR small bowel adenocarcinoma and prescribed in combination with Opdivo;*
 - d. Uveal melanoma and prescribed as a single agent or in combination with Opdivo;*

**Prior authorization may be required for Opdivo.*
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 12 years;
4. For small cell lung cancer and malignant pleural mesothelioma: Failure of a platinum-containing regimen (e.g. cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;*
- *Prior authorization may be required for platinum-containing regimens*
5. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

H. 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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and 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, Hepatocellular Carcinoma

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

Approval duration: Not applicable

C. Cutaneous Melanoma, Non-Small Cell Lung Cancer (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy 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, b, or c):*
 - a. For cutaneous melanoma: New dose does not exceed 10 mg/kg per dose;

- b. For NSCLC: New dose does not exceed 1 mg/kg IV every 6 weeks in combination with Opdivo;
- c. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 12 months or up to a total duration of 3 years (cutaneous melanoma) or 2 years (NSCLC), whichever is less

D. NCCN Compendium Indications (off-label) (must meet all):

1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Yervoy for a covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. Dose is within FDA maximum limit for any FDA-approved indication or is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).*

**Prescribed regimen must be FDA-approved or recommended by NCCN*

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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and 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.CPA.09 for commercial, HIM.PHAR.21 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

ALK: anaplastic lymphoma kinase

BRAF: B-Raf proto-oncogene, serine/threonine kinase

CRC: colorectal cancer

CTLA-4: cytotoxic T-lymphocyte antigen 4

dMMR: mismatch repair deficient

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

HCC: hepatocellular carcinoma

MET: mesenchymal-epithelial transition

MSI-H: microsatellite instability-high

PD-1: programmed death-1

PD-L1: programmed death-ligand 1

RET: rearranged during transfection

ROS1: ROS proto-oncogene 1

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.

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|--|--|--|
| Opdivo [®] (nivolumab) | <p>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</p> <p>Small cell lung cancer 1 mg/kg to 3 mg/kg IV every 2 weeks with or without ipilimumab</p> <p>MSI-H/dMMR CRC 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>MSI-H/dMMR Small bowel adenocarcinoma 3 mg/kg IV once every 3 weeks for four doses, then 3 mg/kg IV or 240 mg IV every 2 weeks with or without ipilimumab</p> <p>Hepatocellular carcinoma 1 mg/kg IV, followed by ipilimumab 3 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 or 480 mg IV every 4 weeks until disease progression or unacceptable toxicity</p> | <p>RCC, SCLC, HCC: 480 mg/dose</p> <p>CRC, small bowel adenocarcinoma: 240 mg/dose</p> |
| cisplatin- or carboplatin-containing regimen | <p>Small cell lung cancer, malignant pleural mesothelioma Varies</p> | Varies |
| Nexavar [®] (sorafenib) | <p>Hepatocellular carcinoma 400 mg PO BID</p> | 800 mg/day |
| platinum-doublet chemotherapy | <p>NSCLC – squamous cell carcinoma paclitaxel + carboplatin dose varies</p> <p>NSCLC – nonsquamous cell carcinoma pemetrexed + [carboplatin or cisplatin]</p> | Varies |

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|-----------|----------------|-----------------------------|
| | dose 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 and Boxed Warnings

- Bristol-Myers Squibb was released from the REMS program for Yervoy in March 2015.
- Boxed warning(s): immune-mediated adverse reactions
- Contraindication(s): none reported

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 or until intolerable toxicity or disease progression, then nivolumab 240 mg IV every 2 weeks or 480 mg IV every 4 weeks | 1 mg/kg/dose |
| Hepatocellular carcinoma | Nivolumab 1 mg/kg IV, followed by ipilimumab 3 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 | 3 mg/kg/dose |
| Metastatic NSCLC | <u>In combination with nivolumab:</u> nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until | 1 mg/kg/dose |

| Indication | Dosing Regimen | Maximum Dose |
|------------|--|--------------|
| | <p>disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression</p> <p><u>In combination with nivolumab and platinum-doublet chemotherapy:</u> nivolumab 360 mg IV every 3 weeks and ipilimumab 1 mg/kg IV every 6 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression</p> | |

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; May 2020. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed June 1, 2020.
2. Ipilimumab. In: National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed June 16, 2020.
3. National Comprehensive Cancer Network. Malignant Pleural Mesothelioma Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed February 17, 2020.
4. National Comprehensive Cancer Network. Small Bowel Adenocarcinoma Version 1.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf. Accessed February 17, 2020.
5. National Comprehensive Cancer Network. Uveal Melanoma Version 1.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf. Accessed February 17, 2020.
6. National Comprehensive Cancer Network. Non-Small Cell Lung Cancer Version 6.2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed June 15, 2020.
7. Hellman MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non-small-cell lung cancer. N Engl J Med. 2019 November; 381(21):2020-2031.

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 ≥ 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 |
| 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 |
| 2Q 2019 annual review: added coverage for malignant pleural mesothelioma; references reviewed and updated. | 02.05.19 | 05.19 |
| 2Q 2020 annual review: added commercial line of business and revised HIM-medical benefit to HIM line of business; added NCCN compendium-supported indications of small bowel adenocarcinoma and uveal melanoma; condensed NCCN compendium-supported indications into one subsection; references reviewed and updated. | 02.16.20 | 05.20 |
| Added FDA-labeled indications of HCC and NSCLC in combination with Opdivo; references reviewed and updated. | 06.23.20 | 08.20 |

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

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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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