Clinical Policy: Ipilimumab (Yervoy)
Reference Number: CP.PHAR.319
Effective Date: 04.17.18
Last Review Date: 05.20
Line of Business: Commercial, HIM, Medicaid

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

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 ≥ 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 ≥ 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 ≥ 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):
   6. Dose does not exceed 1 mg/kg IV every 3 weeks for a maximum of 4 doses;
      a. 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)

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 ≥ 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).

   Approval duration: 16 weeks (maximum of 4 doses)

E. 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 prescribed in combination with Opdivo;*
      b. Malignant pleural mesothelioma prescribed in combination with Opdivo;*
      c. MSI-H or dMMR small bowel adenocarcinoma prescribed in combination with
         Opdivo;*
d. Uveal melanoma prescribed either as a single agent or in combination with Opdivo;*  
*Prior authorization may be required.
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 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**

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

**Approval duration: 12 months or up to a total duration of 3 years, 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
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.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opdivo® (nivolumab)</td>
<td>Renal cell carcinoma&lt;br&gt;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</td>
<td>RCC, SCLC: 480 mg/dose&lt;br&gt;CRC, small bowel adenocarcinoma: 240 mg/dose</td>
</tr>
</tbody>
</table>
### Drug Name

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Regimen</th>
<th>Dose Limit/ Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>1 mg/kg to 3 mg/kg IV every 2 weeks with or without ipilimumab</td>
<td></td>
</tr>
<tr>
<td><strong>MSI-H/dMMR CRC</strong></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>MSI-H/dMMR Small bowel adenocarcinoma</strong></td>
<td>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</td>
<td></td>
</tr>
<tr>
<td>cisplatin- or carboplatin-containing regimen</td>
<td><strong>Small cell lung cancer, malignant pleural mesothelioma</strong></td>
<td>Varies</td>
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</tbody>
</table>

*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.*

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### 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
- Contraindiation(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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous melanoma</td>
<td>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.</td>
<td>10 mg/kg/dose</td>
</tr>
<tr>
<td>Unresectable or metastatic melanoma or small cell lung cancer</td>
<td>3 mg/kg IV every 3 weeks for a total of 4 doses</td>
<td>3 mg/kg/dose</td>
</tr>
</tbody>
</table>
### Indication

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced renal cell carcinoma</td>
<td>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</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>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</td>
<td>1 mg/kg/dose</td>
</tr>
</tbody>
</table>

### VI. Product Availability

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

### VII. References


### 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.

<table>
<thead>
<tr>
<th>HCPCS Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>J9228</td>
<td>Injection, ipilimumab, 1 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy split from CP.PHAR.182 Excellus Oncology. Off-label NCCN recommended uses added.</td>
<td>01.17</td>
<td>03.17</td>
</tr>
<tr>
<td>Added age limit of ≥ 12 years per package labeling.</td>
<td>08.29.17</td>
<td>11.17</td>
</tr>
</tbody>
</table>
## Reviews, Revisions, and Approvals

<table>
<thead>
<tr>
<th>Date</th>
<th>P&amp;T Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>07.24.18</td>
<td>08.18</td>
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**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.

**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.

**2Q 2019 annual review:** added coverage for malignant pleural mesothelioma; references reviewed and updated.

**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.

## 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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