Description
Ipilimumab (Yervoy®) is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody.

FDA Approved Indication(s)
Yervoy is indicated for:

- **Melanoma**
  - 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

- **Renal cell carcinoma (RCC)**
  - Treatment of patients with intermediate or poor risk, previously untreated advanced RCC, in combination with nivolumab

- **Colorectal cancer (CRC)**
  - Treatment of adult and pediatric patients 12 years of age and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab*

- **Hepatocellular carcinoma (HCC)**
  - In combination with nivolumab, the treatment of patients with HCC who have been previously treated with sorafenib*

- **Non-small cell lung cancer (NSCLC)**
  - In combination with nivolumab, for the first-line treatment of adult patients with metastatic NSCLC whose tumors express programmed death-ligand 1 (PD-L1) ≥ 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

- **Malignant pleural mesothelioma**
  - Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab

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*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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ that Yervoy is medically necessary when the following criteria are met:
I. Initial Approval Criteria

A. Melanoma (must meet all):
   1. Diagnosis of unresectable, metastatic, or lymph node positive melanoma;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 12 years;
   4. Request meets one of the following (a, b, or c):*
      a. Unresectable or metastatic disease: Dose does not exceed 10 mg/kg;
      b. Adjuvant treatment: Dose does not exceed 3 mg/kg per dose for a maximum of 4 doses over 16 weeks;
      c. 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. Renal Cell Carcinoma (must meet all):
   1. Diagnosis of RCC;
   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):*
      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)

C. Colorectal Cancer (must meet all):
   1. Diagnosis of MSI-H or dMMR CRC;
   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).

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

Approval duration: 16 weeks (maximum of 4 doses)

D. Hepatocellular Carcinoma (must meet all):
   1. Diagnosis of HCC;
   2. Prescribed by or in consultation with an oncologist;
   3. Age ≥ 18 years;
   4. Member has previously received Nexavar® or Lenvima®;

   *Prior authorization may be required for Nexavar and Lenvima

   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)
E. 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 ≥ 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, b, c, or d):*  
   a. For use in combination with Opdivo for tumors positive for the Tumor Mutation Burden (TMB) biomarker;  
   b. Disease mutation status is unknown or negative for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, and RET, and member has not received prior systemic therapy for advanced disease;  
   c. Disease mutation status is positive for EGFR, ALK, ROS1, BRAF, MET exon 14 skipping, RET, or NTRK gene fusion, and member has received mutation-specific treatment;  
   d. Disease is positive for a RET rearrangement;  
   *Prior authorization may be required for Opdivo*
7. Request meets one of the following (a or b):  
   a. Member has PD-L1 tumor expression of ≥ 1%;  
   b. Yervoy is being used in combination with Opdivo ± a platinum-based regimen (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*

Approval duration: 6 months

F. Malignant Pleural Mesothelioma (must meet all):
1. Diagnosis of unresectable malignant pleural mesothelioma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 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 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*

Approval duration: 6 months

G. NCCN Compendium Indications (off-label) (must meet all):
1. Diagnosis of one of the following (a, b, or c):  
   a. Small cell lung cancer (SCLC);  
   b. MSI-H or dMMR small bowel adenocarcinoma;  
   c. Uveal melanoma;  
2. Prescribed by or in consultation with an oncologist;  
3. Age ≥ 12 years;  
4. For SCLC or MSI-H/dMMR small bowel adenocarcinoma: Prescribed in combination with Opdivo;*  
5. For uveal melanoma: Prescribed as a single agent or in combination with Opdivo;*  
   *Prior authorization may be required for Opdivo.
6. For SCLC: Failure of a platinum-containing regimen (e.g. cisplatin, carboplatin), unless clinically significant adverse effects are experienced or all are contraindicated;
7. 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 ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy
A. Melanoma - Unresectable or Metastatic
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. Melanoma (Adjuvant Treatment), Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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. If request is for a dose increase, request meets one of the following (a, b, or c):
   a. For melanoma: New dose does not exceed 10 mg/kg per dose;
   b. For NSCLC and malignant pleural mesothelioma: 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, malignant pleural mesothelioma), whichever is less

D. NCCN Compendium Indications (off-label) (must meet all):
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions, 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 a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.

Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).
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 policy – ERX.PA.01 or
evidence of coverage documents.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

<table>
<thead>
<tr>
<th>Abbreviation/Acronym</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>ALK</td>
<td>anaplastic lymphoma kinase</td>
</tr>
<tr>
<td>BRAF</td>
<td>B-Raf proto-oncogene, serine/threonine kinase</td>
</tr>
<tr>
<td>CRC</td>
<td>colorectal cancer</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>cytotoxic T-lymphocyte antigen 4</td>
</tr>
<tr>
<td>dMMR</td>
<td>mismatch repair deficient</td>
</tr>
<tr>
<td>EGFR</td>
<td>epidermal growth factor receptor</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<tr>
<td>MET</td>
<td>mesenchymal-epithelial transition</td>
</tr>
<tr>
<td>MSI-H</td>
<td>microsatellite instability-high</td>
</tr>
<tr>
<td>PD-1</td>
<td>programmed death-1</td>
</tr>
<tr>
<td>PD-L1</td>
<td>programmed death-ligand 1</td>
</tr>
<tr>
<td>RCC</td>
<td>renal cell carcinoma</td>
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<tr>
<td>ROS1</td>
<td>ROS proto-oncogene 1</td>
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<tr>
<td>SCLC</td>
<td>small cell lung cancer</td>
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<tr>
<td>TMB</td>
<td>Tumor Mutation Burden</td>
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</table>

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>SCLC 1 mg/kg to 3 mg/kg IV every 2 weeks with or without ipilimumab</td>
<td>RCC, SCLC, HCC: 480 mg/dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CRC, small bowel adenocarcinoma: 240 mg/dose</td>
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<tr>
<td></td>
<td><strong>MSI-H/dMMR Small bowel adenocarcinoma</strong></td>
<td></td>
</tr>
<tr>
<td></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>
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</tr>
<tr>
<td>cisplatin- or carboplatin-containing regimen</td>
<td>SCLC Varies</td>
<td>Varies</td>
</tr>
<tr>
<td>Nexavar (sorafenib)</td>
<td>HCC 400 mg PO BID</td>
<td>800 mg/day</td>
</tr>
<tr>
<td>Lenvima (lenvatinib)</td>
<td>HCC 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients &lt; 60 kg)</td>
<td>12 mg/day</td>
</tr>
<tr>
<td>platinum-containing regimens</td>
<td>NSCLC – squamous cell carcinoma paclitaxel + carboplatin dose varies</td>
<td>Varies</td>
</tr>
<tr>
<td></td>
<td><strong>NSCLC – nonsquamous cell carcinoma</strong></td>
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<tr>
<td></td>
<td>pemetrexed + [carboplatin or cisplatin] dose varies</td>
<td></td>
</tr>
</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.

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dosing Regimen</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma (adjuvant treatment)</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>Melanoma (unresectable or metastatic)</td>
<td>3 mg/kg IV every 3 weeks for a total of 4 doses</td>
<td>3 mg/kg/dose</td>
</tr>
<tr>
<td>RCC</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>CRC</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 or until intolerable toxicity or disease progression, 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>HCC</td>
<td>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</td>
<td>3 mg/kg/dose</td>
</tr>
<tr>
<td>NSCLC</td>
<td>In combination with nivolumab: nivolumab 3 mg/kg IV every 2 weeks and ipilimumab 1 mg/kg IV every 6 weeks until disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression.</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>In combination with nivolumab and platinum-doublet chemotherapy: 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.</td>
<td>1 mg/kg/dose</td>
</tr>
<tr>
<td>Malignant pleural mesothelioma</td>
<td>1 mg/kg every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.</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


<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Date</th>
<th>P&amp;T Approval Date</th>
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<tbody>
<tr>
<td>Policy created</td>
<td>12.04.20</td>
<td>02.21</td>
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</tbody>
</table>

**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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.

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