


Prior Authorization Review Panel

CHC-MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: PA Health & Wellness	Submission Date: 02/01/2021
Policy Number: PA.CP.PHAR.319	Effective Date: 01/2018 Revision Date: 01/2021
Policy Name: Ipilimumab (Yervoy)	
<p>Type of Submission – <u>Check all that apply:</u></p> <p> <input type="checkbox"/> New Policy <input checked="" type="checkbox"/> Revised Policy* <input type="checkbox"/> Annual Review - No Revisions <input type="checkbox"/> Statewide PDL - <i>Select this box when submitting policies for Statewide PDL implementation and when submitting policies for drug classes included on the Statewide PDL.</i> </p>	
<p>*All revisions to the policy <u>must</u> be highlighted using track changes throughout the document.</p> <p>Please provide any changes or clarifying information for the policy below:</p> <p>FDA approved malignant pleural mesothelioma added. Ad hoc changes: melanoma unresectable/metastatic disease and lymph node positive disease criteria sets combined; for HCC, Lenvima added as a prior therapy option per NCCN; for NSCLC, single agent therapy for TMB positive tumor added and combination therapy for RET rearrangement added per NCCN, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen to accommodate NCCN recommended uses; references reviewed and updated.</p>	
<p>Name of Authorized Individual (Please type or print):</p> <p>Auren Weinberg, MD</p>	<p>Signature of Authorized Individual:</p> 

Clinical Policy: Ipilimumab (Yervoy)

Reference Number: PA.CP.PHAR.319

Effective Date: 01/2018

Last Review Date: 01/2021

[Coding Implications](#)
[Revision Log](#)

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) $\geq 1\%$ 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
- **Malignant pleural mesothelioma**
 - Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment 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 Pennsylvania Health and Wellness® 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, lymph node positive, or recurrent melanoma;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 12 years;
4. Request meets one of the following (a, b or c):
 - a. Unresectable or metastatic disease: Dose does not exceed 10 mg per 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*).

Approval duration: 6 months

B. 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*).

Approval duration: 16 weeks (maximum of 4 doses)

C. 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 advanced, progressive, 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)

D. Hepatocellular Cancer (HCC) (must meet all):

1. Diagnosis of HCC;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 12 years;
4. Member has been previously treated with sorafenib (Nexavar) or lenvatinib (Lenvima);

**Prior authorization may be required for sorafenib or lenvatinib.*

5. Prescribed in combination with nivolumab (Opdivo);
**Prior authorization may be required for Opdivo*
6. 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*).

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 \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, 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 \geq 1%;
 - b. Yervoy is being used in combination with Opdivo \pm 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*).

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 \geq 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*).

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 (SCLC);
 - b. MSI-H or dMMR small bowel adenocarcinoma;
 - c. Uveal melanoma;
 - d. Other NCCN recommendations listed as category 1, 2A, or 2B;
2. Prescribed by or in consultation with an oncologist;
3. Age \geq 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;*,*
**Prior authorization may be required for platinum-containing regimens*
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*).

Approval duration: 6 months

H. Other diagnoses/indications: Refer to PA.CP.PMN.53

II. Continued Approval

A. Melanoma-Unresectable or Metastatic

1. Reauthorization beyond 16 weeks is not permitted. Members will need to be re-evaluated against the initial approval criteria, at a minimum of 3 months since initial treatment discontinuation.
 - a. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
 - b. Member is responding positively to therapy.

B. Renal Cell Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma (must meet all):

1. Reauthorization beyond 16 weeks is not permitted. Members will need to be re-evaluated against the initial approval criteria.
 - a. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies;
 - b. Member is responding positively to therapy.

C. Melanoma (Adjuvant Treatment), Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma (must meet all):

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
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*).

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 Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or
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*).

Approval duration: 12 months

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

1. Currently receiving medication via Pennsylvania Health and Wellness benefit and documentation supports positive response to therapy; or the Continuity of Care policy (PA.LTSS.PHAR.01) applies; or

Approval duration: Duration of request or 6 months (whichever is less); or

2. Refer to PA.CP.PMN.53

III. 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

Appendix B: Therapeutic Alternatives

HCC: hepatocellular carcinoma

MET: mesenchymal-epithelial transition

MSI-H: microsatellite instability-high

PD-1: programmed death-1

PD-L1: programmed death-ligand 1

RCC: renal cell carcinoma

ROS1: ROS proto-oncogene 1

SCLC: small cell lung cancer

TMB: Tumor Mutation Burden

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

IV. Dosage and Administration

Indication	Dosing Regimen	Maximum Dose
Melanoma (adjuvant treatment)	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
Melanoma (unresectable or metastatic)	3 mg/kg IV every 3 weeks for a total of 4 doses	3 mg/kg/dose
RCC	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
CRC	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
HCC	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
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 disease progression, unacceptable toxicity, or for up to 2 years in patients without disease progression <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	1 mg/kg/dose
Malignant pleural mesothelioma	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.	1 mg/kg/dose

V. Product Availability

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

VI. References

1. Yervoy Prescribing information. Princeton, NJ: Bristol-Myers Squibb Company; November 2020. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed November 18, 2020.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at: http://www.nccn.org/professionals/drug_compendium. Accessed November 18, 2020.
3. National Comprehensive Cancer Network. Malignant Pleural Mesothelioma Version 2.2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/mpm.pdf. Accessed November 18, 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	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.	05.18	

Reviews, Revisions, and Approvals	Date	Approval Date
2Q 2019 annual review: criteria added for colorectal cancer in combination with nivolumab; added coverage for malignant pleural mesothelioma; references reviewed and updated.	04.19	
2Q 2020 annual review: criteria added for hepatocellular carcinoma (HCC) in combination with nivolumab; added NCCN compendium-supported indications of small bowel adenocarcinoma, uveal melanoma, non-small cell lung cancer; condensed NCCN compendium-supported indications into one subsection; references reviewed and updated.	04/2020	
FDA approved malignant pleural mesothelioma added. Ad hoc changes: melanoma unresectable/metastatic disease and lymph node positive disease criteria sets combined; for HCC, Lenvima added as a prior therapy option per NCCN; for NSCLC, single agent therapy for TMB positive tumor added and combination therapy for RET rearrangement added per NCCN, combination therapy changed from Yervoy and platinum doublet therapy to Yervoy plus/minus a platinum based regimen to accommodate NCCN recommended uses; references reviewed and updated.	01/2021	