

Clinical Policy: Ipilimumab (Yervoy)

Reference Number: LA.PHAR.319

Effective Date: ~~11.03.24~~ ~~07-01-22~~

Last Review Date: ~~06.11.24~~ ~~06-02-23~~

Line of Business: Medicaid

[Coding Implications](#)

[Revision Log](#)

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

****Please note: This policy is for medical benefit****

Description

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

FDA Approved Indication(s)

Yervoy is indicated for:

- **Unresectable or metastatic melanoma**
 - Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab
- **Adjuvant treatment of melanoma**
 - ~~Patients~~ **Adult 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 ~~advance~~ **advanced** renal cell carcinoma, as first-line treatment 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**

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- Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab
- **Esophageal cancer**
 - Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma (ESCC), as first line treatment in combination with nivolumab

*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 Louisiana HealthCare Connections® 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~~;~~ and disease meets one of the following (a or b):
 - a. Unresectable or metastatic;
 - b. Resectable, limited resectable, or lymph node positive;
2. Prescribed by or in consultation with an oncologist;
3. Age is one of the following (a or b):
 - a. For unresectable or metastatic disease: ≥ 12 years;
 - b. For adjuvant treatment: ≥ 18 years;
4. Prescribed in one of the following ways (a, b, or bc):
 - a. As a single agent;
 - b. In combination with Opdivo^{®*} ~~for unresectable or metastatic melanoma^{®*}~~;
 - c. In combination with Keytruda^{®*} ~~for unresectable or metastatic melanoma^{®*}~~ or ~~;~~

**Prior authorization may be required for Opdivo and Keytruda*
5. Request meets one of the following (a, b, or c):*
 - a. Unresectable or metastatic disease: Dose does not exceed 3 mg per kg every 3 weeks for a maximum of 4 doses;
 - b. Adjuvant treatment: Dose does not exceed 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years;
 - 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 advanced or metastatic RCC;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in combination with Opdivo;*

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**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; or CRC with one of the following mutations (a, b, or c):
 - a. MSI-H;
 - b. dMMR;
 - c. Polymerase epsilon/delta (POLE/POLD1);
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*;
**Prior authorization may be required for 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 \geq 18 years;
4. Member has previously received Nexavar®, Lenvima®, or Tecentriq® + bevacizumab (Myasi® and Zirabev™ are preferred), or Imfinzi®;
**Prior authorization may be required for Nexavar, Lenvima, Tecentriq, bevacizumab, and Imfinzi*
5. Prescribed in combination with Opdivo;
**Prior authorization may be required for Opdivo*
6. Documentation of Child-Pugh Class A status;
7. 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 \geq 18 years;

4. Prescribed in combination with Opdivo;*
**Prior authorization may be required for Opdivo*
5. Member ~~has~~does not ~~previously progressed on~~have contraindications to PD-1/PD-L1 inhibitor therapy (e.g., Opdivo, Keytruda, Tecentriq, Imfinzi) (*see Appendix D*);
6. Request meets one of the following (a, b, c, d, e, or f):
 - a. Disease mutation status is negative for actionable biomarkers (EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, ~~AND~~ and ERBB2 [HER2]), and member has not received prior systemic therapy for advanced disease;
 - b. Disease mutation status is positive for EGFR S768I, L861Q, and/or G719X, and member has received prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib;*
 - c. Disease mutation status is positive for EGFR exon 19 deletion or L858R, and member has received prior erlotinib \pm (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib;*
 - d. Disease mutation status is positive for ROS1 rearrangement, and member has received prior crizotinib, entrectinib, ~~or repotrectinib~~, ceritinib, or lorlatinib;*
 - e. Disease mutation status is positive for ALK rearrangement, and member has received prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib;*
 - f. Disease mutation status is positive for EGFR exon 20, KRAS G12C, NTRK1/2/3, BRAF V600E, MET exon 14 skipping, RET rearrangement, or ERBB2 (HER2);
**Prior authorization may be required*
7. 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 \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*).**Prescribed regimen must be FDA-approved or recommended by NCCN*

Approval duration: 6 months

G. Esophageal Cancer (must meet all):

1. Diagnosis of unresectable advanced or metastatic ESCC;
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.*

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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

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

1. Diagnosis of one of the following (a-~~f~~-~~k~~):
 - a. MSI-H or dMMR small bowel adenocarcinoma;
 - ~~b. Metastatic uveal melanoma;~~
 - ~~e-b.~~ MSI-H or dMMR ampullary adenocarcinoma;
 - ~~c. MSI-H or dMMR gastric cancer;~~
 - ~~d. MSI-H or dMMR esophageal adenocarcinoma;~~
 - ~~e. Metastatic or unresectable uveal melanoma;~~
 - ~~d-f.~~ Bone cancer (e.g., chondrosarcoma, osteosarcoma, chordoma, Ewing sarcoma), and both of the following (i and ii):
 - i. Disease is unresectable or metastatic with tissue tumor mutation burden-high tumors with 10 or more mutations per megabase;
 - ii. Disease has progressed following prior treatment and no satisfactory alternative treatment options exist;
 - ~~e-g.~~ BRAF non-specific melanoma brain metastases;
 - ~~f-h.~~ Classic Kaposi sarcoma as subsequent systemic therapy;
 - ~~i. Biliary tract cancer (e.g., gallbladder, intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma), as subsequent therapy;~~
 - ~~j. Merkel cell carcinoma;~~
 - ~~k. Soft tissue sarcoma and one of the following (i or ii):~~
 - ~~i. Disease is angiosarcoma;~~
 - ~~ii. Prescribed as subsequent therapy for advanced or metastatic disease, and disease is one of the following (1-6):~~
 - ~~1) Tumor mutation burden-high (≥ 10 mutations per megabase);~~
 - ~~2) Myxofibrosarcoma;~~
 - ~~3) Undifferentiated pleomorphic sarcoma;~~
 - ~~4) Dedifferentiated liposarcoma;~~
 - ~~5) Cutaneous angiosarcoma;~~
 - ~~6) Undifferentiated sarcomas;~~
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 12 years;
4. Prescribed in combination with Opdivo for all of the following (a-~~d~~-~~g~~):*
 - a. MSI-H/dMMR small bowel adenocarcinoma;
 - b. MSI-H/dMMR ampullary adenocarcinoma;
 - ~~c. MSI-H or dMMR gastric cancer;~~
 - ~~d. MSI-H or dMMR esophageal adenocarcinoma;~~
 - ~~e-e.~~ Bone cancer;
 - ~~d-f.~~ Classic Kaposi sarcoma;

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- g. ~~For uveal melanoma; Biliary tract cancer;~~
5. Prescribed as a single agent or in combination with Opdivo;* for all of the following (a-d):*
a. Uveal melanoma;
b. Brain metastases;
c. Merkel cell carcinoma;
d. Soft tissue sarcoma

**Prior authorization may be required for Opdivo*

6. 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

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

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

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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

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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

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

1. Currently receiving medication via Louisiana Healthcare Connections 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 melanoma: New dose does not exceed 10 mg/kg every 12 weeks for up to 3 years;
 - b. For NSCLC, malignant pleural mesothelioma, and ESCC: 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, ESCC), whichever is less

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

1. Currently receiving medication via Louisiana Healthcare Connections 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. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to LA.PMN.255
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy LA.PMN.53

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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 LA.PMN.53

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
RCC: renal cell carcinoma
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.

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Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Opdivo (nivolumab)	<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>Unresectable or metastatic melanoma <u>Adult and pediatric weighing ≥ 40 kg:</u> nivolumab 1 mg/kg every 3 weeks for four doses in combination with ipilimumab 3 mg/kg every 3 weeks, then nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks as a single agent until disease progression or unacceptable toxicity</p> <p><u>Pediatric weighing < 40 kg:</u> nivolumab 1 mg/kg every 3 weeks for four doses in combination with ipilimumab 3 mg/kg every 3 weeks, then nivolumab 3 mg/kg every 3 weeks or 6 mg/kg mg every 6 weeks as a single agent until disease progression or unacceptable toxicity</p>	<p>RCC, HCC, melanoma: 480 mg/dose</p> <p>CRC, small bowel adenocarcinoma, pediatric (weighing < 40 kg) melanoma: 240 mg/dose</p>
Keytruda (pembrolizumab)	<p>Melanoma Adult: 200 mg every 3 weeks or 400 mg every 6 weeks Pediatric: 2 mg/kg (up to 200 mg) every 3 weeks</p>	See regimen
Nexavar (sorafenib)	<p>HCC 400 mg PO BID</p>	800 mg/day
Lenvima (lenvatinib)	<p>HCC 12 mg PO QD (patients ≥ 60 kg) or 8 mg PO QD (patients < 60 kg)</p>	12 mg/day
Tecentriq (atezolizumab) + bevacizumab (Avastin [®] , Mvasi, Zirabev)	<p>HCC Tecentriq: 840 mg IV every 2 weeks, 1,200 mg IV every 3 weeks, or 1,680 mg IV every 4 weeks Bevacizumab: 15 mg/kg IV every 3 weeks</p>	See regimen
Imfinzi (durvalumab)*	<p>HCC Varies</p>	Varies
platinum- containing regimens	<p>NSCLC – squamous cell carcinoma paclitaxel + carboplatin dose varies</p> <p>NSCLC – nonsquamous cell carcinoma</p>	Varies

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	pemetrexed + [carboplatin or cisplatin] dose varies	
EGFR S768I, L861Q, and/or G719X targeted therapies: afatinib, osimertinib, erlotinib, gefitinib, dacomitinib	NSCLC Varies	Varies
ROS1 targeted therapies: crizotinib, entrectinib, ceritinib	NSCLC 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.

*Off-label

Appendix C: Contraindications and Boxed Warnings

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

Appendix D: General Information

- NCCN no longer recommends the use of Yervoy for the following indications:
 - Small cell lung cancer
 - Tumor mutation burden NSCLC
 - Cutaneous melanoma, as adjuvant systemic therapy in combination with Opdivo if no evidence of disease following metastasis-directed therapy or systemic therapy for oligometastatic disease
 - Colon cancer for patients who are not appropriate for intensive therapy
- Per NCCN, contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, or presence of an oncogene (i.e., EGFR exon 19 deletion or L858R, ALK rearrangements), which would predict lack of benefit.

V. Dosage and Administration

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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)	<u>Monotherapy</u> : 3 mg/kg IV every 3 weeks for a total of 4 doses <u>In combination with nivolumab</u> : 3 mg/kg every 3 weeks with nivolumab 1 mg/kg for a maximum of 4 doses or until unacceptable toxicity, whichever occurs earlier.	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
ESCC	1 mg/kg every 6 weeks with nivolumab 3 mg/kg every 2 weeks or 360 mg every 3 weeks until	1 mg/kg/dose

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Indication	Dosing Regimen	Maximum Dose
	disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.	

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; ~~March~~February 2023. Available at: https://packageinserts.bms.com/pi/pi_yervoy.pdf. Accessed ~~March 16, 2023~~February 7, 2024.
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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-

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date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

HCPSC Codes	Description
J9228	Injection, ipilimumab, 1 mg

Reviews, Revisions, and Approvals	Date	LDH Approval Date
Converted corporate to local policy	04.22	07.01.22
Criteria added for new FDA approved indication of ESCC in combination with Opdivo; for HCC, added additional option for prior use of Imfinzi and removed requirement for no previous treatment with a checkpoint inhibitor per latest NCCN guidelines. For melanoma clarified combination use with Keytruda and removed combination use with Imlygic per NCCN 2B recommendation; updated FDA indication for RCC to mirror PI; revised NSCLC criteria to include additional requirements related to mutation status, added off-label use for MSI-H/dMMR ampullary adenocarcinoma, bone cancer, brain metastases, and Kaposi sarcoma per NCCN compendium; Updated criteria for melanoma to reflect FDA approved pediatric age extension for use in combination with Opdivo and updated appendix B; <u>references reviewed and updated.</u> <u>References reviewed and updated:</u> <u>Annual review: for melanoma, added criteria for resectable and limited resectable per NCCN 2A recommendations, removed specification to use combination Opdivo/Yervoy for only unresectable or metastatic melanoma; for colorectal cancer, added indication of POLE/POLD1 mutation per NCCN; for NSCLC ROS1 rearrangement, added reprotrectinib and lorlatinib as prior use option per NCCN; for malignant pleural mesothelioma, revised criteria to allow both unresectable and resectable disease per NCCN; for off-label NCCN compendium indication, added the following indications: MSI-H or dMMR gastric cancer, MSI-H or dMMR esophageal adenocarcinoma, biliary tract cancers, merkel cell carcinoma, and soft tissue sarcoma; references reviewed and updated.</u>	06.02.23	<u>10.05.23</u>
	06.11.24	

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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

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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. LHCC 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.

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 LHCC administrative policies and procedures.

This clinical policy is effective as of the date determined by LHCC. 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. LHCC 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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