Drug Policy:

Yervoy™ (ipilimumab)

POLICY NUMBER UM ONC_1201	SUBJECT Yervoy™ (ipilimumab)		DEPT/PROGRAM UM Dept	PAGE 1 of 6
DATES COMMITTEE REVIEWED 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22, 02/08/23, 03/08/23, 05/10/23, 06/12/24, 09/18/24, 01/08/25	**APPROVAL DATE** January 08, 2025	**EFFECTIVE DATE** January 31, 2025	**COMMITTEE APPROVAL DATES** 01/04/12, 10/16/13, 10/14/15, 04/13/16, 02/08/17, 02/14/18, 02/13/19, 12/11/19, 02/12/20, 04/08/20, 06/10/20, 11/11/20, 02/10/21, 04/14/21, 11/15/21, 04/13/22, 05/11/22, 08/10/22, 09/20/22, 11/09/22, 12/16/22, 02/08/23, 03/08/23, 05/10/23, 06/12/24, 09/18/24, 01/08/25	
PRIMARY BUSINESS OWNER: UM		**COMMITTEE/BOARD APPROVAL** Evolent Specialty Services Clinical Guideline Review Committee		
NCQA STANDARDS UM 2		**ADDITIONAL AREAS OF IMPACT**		
CMS REQUIREMENTS	**STATE/FEDERAL REQUIREMENTS**		**APPLICABLE LINES OF BUSINESS** Commercial, Exchange, Medicaid	

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses clinical guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. A list of codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this clinical guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their plan customer service representative for specific coverage information.

I. PURPOSE

To define and describe the accepted indications for Yervoy (ipilimumab) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

II. INDICATIONS FOR USE/INCLUSION CRITERIA

A. Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided:

1. The requested medication was used within the last year, AND
2. The member has not experienced disease progression and/or no intolerance to the requested medication, AND
3. Additional medication(s) are not being added to the continuation request.

B. Colorectal Cancer

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab) for the treatment of adult and pediatric members 12 years and older with microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR), or polymerase epsilon/delta (POLE/POLD1) mutation unresectable, metastatic, or recurrent colorectal cancer.

C. Esophageal Squamous Cell Carcinoma (ESCC)

1. Opdivo (nivolumab) may be used in combination with Yervoy (ipilimumab) as first-line treatment of unresectable advanced/recurrent/metastatic squamous cell esophageal carcinoma, regardless of PD-L1 status.
2. NOTE: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the dose of Yervoy (ipilimumab), supported by Evolent policy, is 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years. When the above combination is used with chemotherapy, chemotherapy may continue until disease progression or unacceptable toxicity.

D. Hepatocellular Carcinoma (HCC)

1. NOTE: Yervoy (ipilimumab) + Opdivo (nivolumab) is not supported by Evolent Policy for the first line treatment of unresectable/metastatic recurrent hepatocellular carcinoma. This policy position is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) showing superior outcomes compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at https://www.evolent.com/pathways.
2. Yervoy (ipilimumab) + Opdivo (nivolumab) may be used as subsequent line therapy for members with unresectable/metastatic hepatocellular carcinoma if the member has not been previously treated with a checkpoint inhibitor. This recommendation is based on the lack of peer-reviewed literature/data to support the use of the above regimen in patients previously treated with a checkpoint inhibitor (e.g., atezolizumab with or without bevacizumab).

E. Malignant Pleural Mesothelioma

1. Yervoy (ipilimumab) may be used in combination with Opdivo (nivolumab), as first line therapy for members with metastatic/unresectable Malignant Pleural Mesothelioma. Evolent policy supports a Yervoy (ipilimumab) dose of 1 mg/kg every 6 weeks; Opdivo (nivolumab) may be dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

F. Melanoma

1. NOTE: Yervoy (ipilimumab) +/- Opdivo (nivolumab) is not supported by Evolent Policy for the adjuvant treatment of resected melanoma. This policy position is based on the results of the CheckMate 915 randomized trial showing inferior outcomes with Yervoy (ipilimumab) + Opdivo (nivolumab) compared to single agent Opdivo (nivolumab). Please refer to Evolent alternative agents/regimens recommended by Evolent, including but not limited to regimens available at http://pathways.newcenturyhealth.com.

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2. The member has cutaneous melanoma and Yervoy (ipilimumab) may be used as any of the following:
    a. For unresectable or metastatic melanoma:
        i. First line therapy in combination with Opdivo (nivolumab) OR
        ii. Second line or subsequent therapy as a single agent or in combination with Opdivo (nivolumab) in members who have not received prior therapy with Yervoy (ipilimumab).
        iii. NOTE: When Opdivo (nivolumab) is used in combination with Yervoy (ipilimumab), the use of Yervoy (ipilimumab) 3 mg/kg is not supported by Evolent Policy. The dose of Yervoy (ipilimumab), supported by Evolent policy, should not exceed 1 mg/kg every 3 weeks for a maximum of 4 cycles with Opdivo (nivolumab) dosed at 3 mg/kg (360 mg) every 3 weeks followed by maintenance Opdivo (nivolumab), the latter may be dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks. The above policy position is based on the results of the CheckMate 511 trial which demonstrated a significantly lower incidence of treatment-related adverse events and equivalent survival with Ipilimumab 1 mg/kg compared to 3 mg/kg, when used in combination with Opdivo (nivolumab) in patients with advanced or metastatic melanoma.
        iv. In brain metastases, Yervoy (ipilimumab) 3 mg/kg in combination with Opdivo (nivolumab) 1 mg/kg every 3 weeks for a maximum of 4 cycles followed by maintenance Opdivo (nivolumab) 240 mg every 2 weeks or 480 mg every 4 weeks is recommended.

G. Non-Small Cell Lung Cancer

1. Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy may be used in metastatic Non- Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression less than 1%.
2. NOTE 1: Yervoy (ipilimumab) + Opdivo (nivolumab) with or without chemotherapy is a not supported by Evolent Policy when used for the treatment of metastatic Non-Small Cell Lung Cancer (both squamous and non-squamous) that is EGFR and ALK negative and has a PDL-1 expression 1% or higher. This policy position is based on the lack of Level 1 Evidence (randomized clinical trials and/or meta-analyses) to show superior outcomes with Yervoy (ipilimumab) + Opdivo (nivolumab), with or without chemotherapy, compared to Evolent recommended alternatives agents/regimens, including but not limited to regimens at http://pathways.newcenturyhealth.com.
3. NOTE 2: The dose of Yervoy (ipilimumab), supported by Evolent policy, should not exceed 1 mg/kg every 6 weeks with Opdivo (nivolumab) dosed at 3 mg/kg (up to 360 mg) every 3 weeks, 240 mg every 2 weeks, or 480 mg every 4 weeks for a maximum of 2 years.

H. Renal Cell Carcinoma

1. The member has a relapsed/metastatic or surgically unresectable disease AND
2. Yervoy (ipilimumab) is being used in combination with Opdivo (nivolumab) for 4 cycles followed by single agent nivolumab for Intermediate or Poor risk disease (as defined by the IMDC criteria).
    a. NOTE: The dose of Yervoy (ipilimumab), supported by Evolent policy, in this setting is 1mg/kg IV every 3 weeks for a total of 4 cycles. Opdivo (nivolumab) may be dosed at 3 mg/kg (up to 360 mg) every 3 weeks for 4 cycles followed by single agent Opdivo (nivolumab) maintenance therapy dosed up to 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks, until disease progression or unacceptable toxicity.

    IMDC Criteria:

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CRITERIA= Assign 1 point for each	RISK CATEGORIES= RISK SCORE
Time to systemic treatment less than 1 year from diagnosis	Favorable Risk = 0
Performance Status < 80% Karnofsky Scale	Intermediate Risk = 1-2
Hemoglobin < LLN; <12 g/dL	Poor Risk= 3-6
Calcium > ULN; > 12 mg/dL	
Neutrophils > ULN	
Platelets > ULN	

III. EXCLUSION CRITERIA

A. Members who experience severe or life-threatening reactions to Yervoy (ipilimumab) including any moderate immune mediated adverse events or symptomatic endocrinopathy.

B. Disease progression during or following treatment with Yervoy (ipilimumab).

C. Dosing exceeds single dose limit of Yervoy (ipilimumab) 3mg/kg when Yervoy is being used as a single agent.

D. Investigational use of Yervoy (ipilimumab) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:

1. Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
2. Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
3. Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.
4. Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
5. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
6. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
7. That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

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IV. CODING INFORMATION

HCPCS Code	Description
J9228	Injection, ipilimumab, 1 mg

V. MEDICATION MANAGEMENT

A. Please refer to the FDA label/package insert and/or ASCO guidelines for management of immunotherapy toxicities.

VI. APPROVAL AUTHORITY

A. Review – Utilization Management Department

B. Final Approval – Utilization Management Committee

VII. ATTACHMENTS

A. None

VIII. REFERENCES

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