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Section:	Prescription Drugs	**Effective Date:**	July 1, 2023
Subsection:	Antineoplastic Agents	**Original Policy Date:**	March 9, 2012
Subject:	Yervoy	**Page:**	1 of 8

Last Review Date: June 15, 2023

Yervoy

Description

Yervoy (ipilimumab)

Background
Yervoy (ipilimumab) is a monoclonal antibody. Yervoy blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen). CTLA-4 may play a role in slowing down or turning off the body's immune system, affecting its ability to fight off cancerous cells. Yervoy may work by allowing the body's immune system to recognize, target, and attack cells in melanoma tumors. The drug is administered intravenously (1-2).

Regulatory Status
FDA-approved indications: Yervoy is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4) blocking antibody indicated for: (1)

1. Melanoma
    a. Treatment of unresectable or metastatic melanoma in adults and pediatric patients 12 years and older as a single agent or in combination with nivolumab
    b. Adjuvant treatment of 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
2. Renal Cell Carcinoma (RCC)
    a. Treatment of adult patients with intermediate or poor risk advanced renal cell carcinoma, as first-line treatment in combination with nivolumab
3. Colorectal Cancer
    a. 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 that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in combination with nivolumab

4. Hepatocellular Carcinoma
    a. Treatment of adult patients with hepatocellular carcinoma who have been previously treated with sorafenib, in combination with nivolumab
5. Non-Small Cell Lung Cancer (NSCLC)
    a. Treatment of adult patients with metastatic non-small cell lung cancer expressing PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, as first-line treatment in combination with nivolumab
    b. Treatment of adult patients with metastatic or recurrent NSCLC with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy
6. Malignant Pleural Mesothelioma
    a. Treatment of adult patients with unresectable malignant pleural mesothelioma, as first-line treatment in combination with nivolumab
7. Esophageal squamous cell carcinoma
    a. Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first-line treatment in combination with nivolumab

Off-Label Uses: (2)

1. Retreatment of melanoma in patients who experience disease control but who relapse or progress greater than 3 months after treatment discontinuation
2. Central nervous system (CNS) metastases if active against primary tumor (melanoma)
3. Small cell lung cancer (SCLC) in combination with nivolumab

Yervoy has a warning regarding severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab. Permanently discontinue Yervoy and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions. Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose (1).

Yervoy is only given for 4 doses with nivolumab for renal cell carcinoma, colorectal cancer, and hepatocellular carcinoma. After that, nivolumab is given as a single agent (1).

Yervoy is only given for up to 2 years for patients with NSCLC and malignant pleural mesothelioma. Yervoy is only given for up to 3 years for patients for the adjuvant treatment of melanoma (1).

Safety and effectiveness of Yervoy for pediatric patients less than 12 years of age have not been established (1).

Related policies
Imjudo, Opdivo

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Yervoy may be considered **medically necessary** if the conditions indicated below are met.

Yervoy may be considered **investigational** for all other indications.

Prior-Approval Requirements

Age 12 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Unresectable or metastatic melanoma

2. Cutaneous melanoma (Stage III)
    a. Used as adjuvant therapy
    b. Pathologic involvement of regional lymph nodes of more than 1 mm
    c. Patient has undergone complete resection, including total lymphadenectomy

3. Central nervous system (CNS) metastases
    a. Yervoy was active against the primary tumor (melanoma)
    b. Member has recurrent disease

4. Small cell lung cancer (SCLC)
    a. Used in combination with nivolumab

5. Unresectable malignant pleural mesothelioma
    a. Used as first-line treatment in combination with nivolumab

6. Advanced renal cell carcinoma
    a. Patient is considered to have an intermediate or poor prognosis
        i. Used in combination with nivolumab

7. Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
    a. Disease progression following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
    b. Diagnosis has to be confirmed by PCR-based assay genetic testing
    c. Used in combination with nivolumab

8. Hepatocellular carcinoma
    a. Prior treatment with sorafenib (Nexavar)
    b. Used in combination with nivolumab

9. Unresectable advanced or metastatic esophageal squamous cell carcinoma
    a. Used as first-line treatment
    b. Used in combination with nivolumab

10. Metastatic non-small cell lung cancer (NSCLC)
    a. **NO** EGFR or ALK genomic tumor aberrations with **ONE** of the following:
        i. Tumors express PD-L1 as determined by an FDA-approved test **AND** used as first-line treatment in combination with nivolumab
        ii. Used as first-line treatment in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy

11. Recurrent non-small cell lung cancer (NSCLC)
    a. **NO** EGFR or ALK genomic tumor aberrations

b. Used as first-line treatment in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy

AND ALL of the following:

1. Clinical chemistries, including adrenocorticotropic hormone (ACTH) level, and liver and thyroid function tests are evaluated at baseline and before each dose
2. Agree to permanently discontinue Yervoy and initiate corticosteroid therapy for severe immune-mediated reactions

Prior – Approval *Renewal* Requirements

Age 12 years of age or older

Diagnoses

Patient must have **ONE** of the following:

1. Cutaneous melanoma (Stage III)
   a. **NO** disease progression or unacceptable toxicity
2. Central nervous system (CNS) metastases
   a. **NO** disease progression or unacceptable toxicity
3. Small cell lung cancer (SCLC)
   a. Used in combination with nivolumab
   b. **NO** disease progression or unacceptable toxicity
4. Unresectable malignant pleural mesothelioma
   a. Used in combination with nivolumab
   b. **NO** disease progression or unacceptable toxicity
5. Unresectable advanced or metastatic esophageal squamous cell carcinoma
   a. Used in combination with nivolumab
   b. **NO** disease progression or unacceptable toxicity
6. Metastatic or recurrent non-small cell lung cancer (NSCLC)
   a. Used in combination with nivolumab
   b. **NO** disease progression or unacceptable toxicity

AND the following:

1. Clinical chemistries, including adrenocorticotropic hormone (ACTH) level, and liver and thyroid function tests are evaluated before each dose

Policy Guidelines

Pre - PA Allowance

None

Prior - Approval Limits

Duration 6 months

Prior – Approval *Renewal* Limits

Duration 18 months

TWO renewals **ONLY** for Adjuvant Treatment of Melanoma

ONE renewal **ONLY** for Esophageal Squamous Cell Carcinoma, NSCLC, or Malignant Pleural Mesothelioma

NO renewal for Unresectable or Metastatic Melanoma, Renal Cell Carcinoma, Colorectal Cancer, or Hepatocellular Carcinoma

Rationale

Summary

Yervoy is a monoclonal antibody. Yervoy has a warning regarding severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. The most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy (1-2).

Prior authorization is required to ensure the safe, clinically appropriate, and cost-effective use of Yervoy while maintaining optimal therapeutic outcomes.

References

1. Yervoy [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; February 2023.
2. NCCN Drugs & Biologics Compendium® Ipilimumab 2023. National Comprehensive Cancer Network, Inc. Accessed on April 18, 2023.

Policy History

Date	Action
January 2011	New Policy
March 2013	Annual editorial and reference update Addition of age requirement of 18 years or older
September 2013	Annual editorial review by the PMPC
December 2014	Annual editorial review by the PMPC Removal of REMS requirement;
June 2015	Annual review and reference update
November 2015	Addition of cutaneous melanoma indication and renewal requirements
March 2016	Annual editorial review Policy number change from 5.04.13 to 5.21.13
June 2016	Annual editorial review and reference update
June 2017	Annual editorial review and reference update Addition of age requirement to Renewal Criteria
August 2017	Addition of central nervous system (CNS) metastases if active against primary tumor (melanoma), malignant pleural mesothelioma and small cell lung cancer. Addition of unresectable or metastatic in renewal section Removal of agreement to permanently discontinue Yervoy if full treatment course is not completed within 16 weeks of administration of first dose for melanoma. Age change from 18 to 12 years of age.
September 2017	Annual review
May 2018	Addition of indication: Intermediate or poor risk, previously untreated advanced renal cell carcinoma, in combination with ipilimumab Addition of monitoring of adrenocorticotropic hormone (ACTH) level to initiation and renewal criteria (per boxed warning in package insert). Addition of renewal requirements to small cell lung cancer (SCLC), and malignant pleural mesothelioma of used in combination with nivolumab (Opdivo)
June 2018	Annual review Removal of the requirement: **no** disease progression or unacceptable toxicity from Unresectable or metastatic melanoma renewal section
July 2018	Addition of indication: microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, in

	combination with nivolumab and changed initiation duration from 4 months to 6 months
September 2018	Annual review
June 2019	Annual review and reference update
April 2020	Addition of indication: hepatocellular carcinoma. Revised renewal requirements to “no renewal for Unresectable or Metastatic Melanoma, Renal Cell Carcinoma, Colorectal Cancer, or Hepatocellular Carcinoma”
May 2020	Addition of indication: metastatic non-small cell lung cancer (NSCLC). Changed renewal duration from 12 months to 18 months. Addition of indication: metastatic or recurrent NSCLC with no EGFR or ALK tumor aberrations as first-line treatment with nivolumab and 2 cycles of platinum-doublet chemotherapy
June 2020	Annual review
October 2020	Per FEP, revised malignant pleural mesothelioma indication: removed from off-label section, added requirement that disease must be unresectable and be used as first-line treatment in combination with nivolumab. Added renewal limits for malignant pleural mesothelioma and adjuvant treatment of melanoma
December 2020	Annual review
December 2021	Annual review and reference update
June 2022	Addition of indication per PI update: unresectable advanced or metastatic esophageal squamous cell carcinoma in combination with nivolumab
September 2022	Annual review and reference update
March 2023	Annual review and reference update
June 2023	Annual editorial review and reference update

Keywords

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on June 15, 2023 and is effective on July 1, 2023.