Department:	Pharmacy Management	**Original Approval:**	10/12/2012
Policy #:	PM103	**Last Approval:**	03/08/2019
Title:	Ipilimumab (Yervoy®)		
Approved By:	UM Pharmacy Subcommittee		

BACKGROUND

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

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.[1]

The safety and efficacy of Ipilimumab were investigated in a randomized (3:1:1), double-blind, double-dummy trial that included 676 randomized patients with unresectable or metastatic melanoma previously treated with one or more of the following: aldesleukin, dacarbazine, temozolomide, fotemustine, or carboplatin.[1]

CONDITIONS WITH APPROVAL

Each authorization period will be for six months.

All requests for Ipilimumab also require referral to CHPW Case Management.

INDICATIONS/CRITERIA

Medicaid Members	***Continue to criteria for approval below.***
Medicare Members	***Step-utilization of Part D drugs not required.***

Ipilimumab is considered Medically Necessary for the following indication:

National Comprehensive Cancer Network (NCCN) Category for Ipilumumab[2]

NCCN Categories of Evidence and Consensus: **Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. **Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. **Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.[2]

NCCN Disease	NCCN Recommended Use	NCCN Category
Central Nervous System Cancers - Limited (1-3) Metastatic Lesions	Treatment for brain metastases in patients with melanoma • in combination with nivolumab for newly diagnosed brain metastases in select patients (eg, patients with small asymptomatic brain metastases) with newly diagnosed or stable systemic disease or reasonable systemic treatment options • in combination with nivolumab for recurrent brain metastases • as a single agent for recurrent brain metastases	2A
Central Nervous System Cancers - Multiple (>3) Metastatic Lesions	Treatment for recurrent brain metastases in patients with melanoma and stable systemic disease or reasonable systemic treatment options • in combination with nivolumab • as a single agent	2A
Colon Cancer	Primary treatment in combination with nivolumab for unresectable metachronous metastases (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months	2A

Colon Cancer	Initial therapy in combination with nivolumab for patients with unresectable advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) who are not appropriate for intensive therapy	2B
Colon Cancer	Subsequent therapy in combination with nivolumab (if no previous treatment with a checkpoint inhibitor) for unresectable advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy	2A
Cutaneous Melanoma	Adjuvant treatment as a high-dose single agent (if prior exposure to nivolumab or pembrolizumab) •following CLND and/or complete resection of nodal recurrence •following complete resection of distant metastatic disease	1 following CLND and/or complete resection of nodal recurrence 2A following complete resection of distant metastatic disease
Cutaneous Melanoma	First-line therapy in combination with nivolumab for metastatic or unresectable disease	1
Cutaneous Melanoma	Second-line or subsequent therapy for metastatic or unresectable disease after disease progression or maximum clinical benefit from BRAF targeted therapy •as a single agent or in combination with nivolumab if checkpoint inhibitor immunotherapy was not previously used •in combination with nivolumab for patients who progress on single agent checkpoint inhibitor immunotherapy •in combination with intralesional injection of talimogene laherparepvec •may be considered as re-induction therapy (as a single agent or in combination with nivolumab) if prior checkpoint inhibitor immunotherapy resulted in disease control	2A for all others 2B for combination with talimogene laherparepvec

	(complete response, partial response, or stable disease) and no residual toxicity, and disease progression/relapse occurred >3 months after treatment discontinuation	
Kidney Cancer	Used in combination with nivolumab for 4 cycles followed by single-agent nivolumab for relapse or stage IV disease •as first-line therapy for clear cell histology and favorable risk •as preferred first-line therapy for clear cell histology and poor/intermediate risk •as preferred subsequent therapy for clear cell histology	1 for first-line therapy for poor/intermediate risk 2A for first-line therapy for favorable risk or for subsequent therapy
Malignant Pleural Mesothelioma	Subsequent systemic therapy in combination with nivolumab	2A
Non-Small Cell Lung Cancer	Activity against tumor mutational burden (TMB) in combination with nivolumab	2A
Rectal Cancer	Primary treatment in combination with nivolumab for unresectable metachronous metastases (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) and previous adjuvant FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CapeOX (capecitabine and oxaliplatin) within the past 12 months	2A
Rectal Cancer	Initial therapy in combination with nivolumab for patients with unresectable advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) who are not appropriate for intensive therapy	2B
Rectal Cancer	Subsequent therapy in combination with nivolumab (if no previous treatment with a checkpoint inhibitor) for unresectable advanced or metastatic disease (deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] only) following previous oxaliplatin- irinotecan- and/or fluoropyrimidine-based therapy	2A
Small Cell Lung Cancer (SCLC)	Subsequent systemic therapy for patients with performance status 0-2 in combination with nivolumab for • relapse within 6 months following complete or partial response or stable disease with initial treatment • primary progressive disease	2A

Uveal Melanoma	Consider for metastatic or unresectable disease •as single-agent therapy •in combination with nivolumab	2A

SPECIAL CONSIDERATIONS

Boxed Warning: YERVOY can result in severe and fatal immune-mediated adverse reactions. 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 YERVOY. 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. Consult the full FDA label with particular attention to boxed warning(s).[1]

LIMITATIONS/EXCLUSIONS

Please refer to a product line's certificate of coverage for benefit limitations and exclusions for these services:

PRODUCT LINE	LINK TO CERTIFICATE OF COVERAGE
MEDICARE ADVANTAGE	http://healthfirst.chpw.org/for-members/resource-library/handbooks-and-guides
WASHINGTON APPLE HEALTH	http://chpw.org/our-plans/apple-health/
INTEGRATED MANAGED CARE	http://chpw.org/our-plans/apple-health/

Citations & References

CFR		
WAC		
RCW		
Contract Citation	☐ WAH	

	☐ IMC	
	☐ MA	
Other Requirements		
NCQA Elements		
References	1. YERVOY® (ipilimumab) injection, for intravenous use [prescribing information]. Princeton, NJ: Bristol-Myers Squibb Company; Revised February 2018. Accessed February 2018. 2. The NCCN Drugs & Biologics Compendium® Ipilimumab © 2018 National Comprehensive Cancer Network, Inc. Available at: https://www.nccn.org/professionals/drug_compendium/content/. Accessed February 25, 2019.	

Revision History

Revision Date	Revision Description	Revision Made By
10/4/2012	Original Draft	Maria Chan, Pharm.D.
10/12/2012	Approval	P&T Committee
10/28/2014	Addition of REMS information	Frances McGaugh, Pharm.D.
11/07/2014	Approval	P&T Committee
10/23/2015	Revision review	Frances McGaugh, Pharm.D.
11/11/2015	Approval	MMLT
05/09/2017	All content updated	Sophia Yun, PharmD
05/19/2017	Approval	MMLT
02/13/2018	Updated revision	Catherine Vu, PharmD
03/01/2018	Approval	MMLT
03/09/2018	Transferred from UM107 to Pharmacy	Cindy Bush
02/25/2019	Updated revision	Jennifer Farley, PharmD
03/08/2019	Approval	UM Pharmacy Subcommittee