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Subject: Ipilimumab (Yervoy™) Injection

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DESCRIPTION:

Ipilimumab (Yervoy™), a recombinant, human monoclonal antibody that binds to the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), was approved by the US Food and Drug Administration (FDA) in March of 2011 for the treatment of metastatic melanoma. Approval was based on the results of a phase III study of subjects with unresectable metastatic disease that progressed during systemic therapy. Subjects were randomized to one of three arms: ipilimumab plus glycoprotein 100 peptide vaccine (gp100), ipilimumab monotherapy, or gp100 monotherapy. Overall survival was significantly prolonged in both arms treated with ipilimumab when compared to the gp100 alone arm (10 months vs. 6.4 months, $p<0.05$). Additionally, subjects achieved partial response or stable disease after ipilimumab re-induction. In a second phase III study, the efficacy and safety of ipilimumab was evaluated as first-line therapy for metastatic melanoma. Subjects were randomized to dacarbazine plus ipilimumab or dacarbazine plus placebo. Subjected treated with ipilimumab had a longer overall survival when compared with those treated with placebo (11.2 vs. 9.1 months); furthermore, treatment with ipilimumab significantly prolonged the 3-year overall survival when compared to placebo (20.8% vs. 12.2%, HR 0.72, $p<0.01$). Ipilimumab is FDA approved as a single agent for 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. The FDA has approved ipilimumab in combination with nivolumab for the treatment of unresectable or metastatic melanoma, previously untreated renal cell carcinoma, and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Current National Comprehensive Cancer Network (NCCN) guidelines for the treatment of melanoma recommend ipilimumab for unresectable or metastatic melanoma and in the adjuvant setting as a high-

dose single agent following use of nivolumab or pembrolizumab and following a complete lymph node dissection, complete resection of nodal recurrence, or complete resection of distant metastatic disease. The NCCN guidelines also provide recommendations for the use of ipilimumab for brain metastases from melanoma, colorectal cancer, kidney cancer, malignant pleural mesothelioma, non-small cell lung cancer, small cell lung cancer, and uveal melanoma.

POSITION STATEMENT:

I. Initiation of treatment with ipilimumab (Yervoy™) meets the definition of **medical necessity** when used to treat **EITHER** of the following:

A. Unresectable or metastatic melanoma when **ALL** of the following are met:

1. Member has not received prior therapy with ipilimumab (for members who have received prior ipilimumab therapy as a single agent, refer to criteria for reinduction).
2. Member meets one of the following:
    a. Ipilimumab is used in combination with nivolumab as first-line therapy
    b. Ipilimumab is used as a single agent as second-line or subsequent therapy for disease progression if not previously used
    c. Ipilimumab is used in combination with nivolumab as second-line or subsequent therapy for disease progression if not previously used
3. The dose does not exceed 3 mg/kg every 3 weeks for a total of 4 doses

B. Adjuvant treatment of melanoma when **ALL** of the following are met:

1. **ONE** of the following;
    a. Member had complete lymph node dissection
    b. Member underwent surgery for disease recurrence and has no evidence of disease following surgery
    c. Member with metastatic disease who had complete resection with no evidence of disease
2. Member previously received anti-PD-1 therapy (e.g., nivolumab, pembrolizumab) in the adjuvant setting
3. Ipilimumab is used as a single agent
4. The dose does not exceed 10 mg/kg every 3 weeks for a total of 4 doses

C. Brain metastases from metastatic melanoma when **ALL** of the following are met:

1. **ONE** of the following:
    a. Ipilimumab is used as a single agent for recurrent brain metastases from melanoma
    b. Ipilimumab is used in combination with nivolumab for recurrent brain metastases from melanoma
    c. Ipilimumab is used in combination with nivolumab for newly diagnosed brain metastases from melanoma
2. The dose does not exceed the following:
    a. Single agent use: 10 mg/kg every 3 weeks for a total of 4 doses
    b. In combination with nivolumab: 3 mg/kg every 3 weeks for a total of 4 doses

D. Colon or Rectal cancer when **ALL** of the following are met:
    1. Member has metastatic or unresectable advanced disease
    2. Tumor is classified as microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR]
    3. The member has not previously received ipilimumab, nivolumab or pembrolizumab therapy
    4. When used for **ONE** of the following
        a. As subsequent therapy following disease progression with oxaliplatin-, irinotecan- or fluoropyrimidine-based therapy
        b. Following adjuvant FOLFOX or CapeOX if received within the previous year
    5. Ipilimumab will be used in combination with nivolumab
    6. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses
E. Kidney cancer when **ALL** of the following are met:
    1. Member is diagnosed with relapsed or stage IV disease
    2. Member meets one of the following:
        a. Ipilimumab is used in combination with nivolumab as first-line therapy for member's with predominant clear cell histology
        b. Ipilimumab is used in combination with nivolumab as subsequent therapy for member's with predominant clear cell histology if not previously used
    3. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses
F. Malignant Pleural Mesothelioma when **ALL** of the following are met:
    1. Ipilimumab will be used as subsequent therapy following disease progression with pemetrexed
    2. Ipilimumab will be used in combination with nivolumab
    3. The dose does not exceed 1 mg/kg every 6 weeks
G. Non-small cell lung cancer when **ALL** of the following are met:
    1. Member's disease is classified as **ONE** of the following:
        a. Metastatic
        b. Mediastinal lymph node recurrence and member has received prior radiation therapy
    2. Member has a high tumor mutational burden (i.e., at least 10 mutations per megabase)
    3. The member has not previously received systemic chemotherapy
    4. Member's ECOG performance status is 0-2
    5. Ipilimumab is used in combination with nivolumab
    6. The dose does not exceed 1 mg/kg every 6 weeks
H. Small cell lung cancer when **ALL** of the following are met:
    1. **ONE** of the following:
        a. Member's disease relapsed within 6 months of initial chemotherapy
        b. Member's disease is progressive on initial chemotherapy

2. Member's ECOG performance status is 0-2
3. Ipilimumab will be used in combination with nivolumab
4. The dose does not exceed 3 mg/kg every 3 weeks for a total of 4 doses

I. Uveal melanoma when **ALL** of the following are met:
1. Member's disease is unresectable or metastatic
2. Ipilimumab will be used as a single agent or in combination with nivolumab
3. The dose does not exceed 3 mg/kg every 3 weeks for a total of 4 doses

J. Other FDA-approved or NCCN supported diagnosis (not previously listed above)
1. **ONE** of the following is met:
a. Member is diagnosed with a condition that is consistent with an indication listed in the product's FDA-approved prescribing information (or package insert) AND member meets any additional requirements listed in the "Indications and Usage" section of the FDA-approved prescribing information (or package insert)
b. Indication **AND** usage is recognized in NCCN Drugs and Biologics Compendium as a Category 1 or 2A recommendation
2. The dose does not exceed the maximum FDA-approved dose

Approval Duration: 4 months (16 weeks)

II. **Reinduction** of ipilimumab therapy for treatment of melanoma **meets the definition of medical necessity** when **ALL** of the following criteria are met:

A. Member has completed initial induction therapy (i.e., completed 4 cycles within a continuous 16 week period)

B. Member's disease relapsed or progressed greater than 3 months after initial clinical response or stable disease (i.e., at least 3 months have passed since week 12 of initial cycle)

C. Member did not have severe systemic toxicity with prior ipilimumab use that requires permanent discontinuation as indicated by **ANY** of the following:
1. Any Grade 2 or higher immune-mediated reactions lasting 6 weeks or longer involving any organ system (CTCAE)
2. Inability to reduce corticosteroid to 7.5 mg prednisone or equivalent per day
3. Any Grade 3 or higher immune-mediated reactions involving any organ system (CTCAE)
4. Opthalmologic reactions not improving to grade 1 within 2 weeks of topical therapy or requiring systemic treatment

D. Member does not have any remaining systemic toxicity with prior ipilimumab use

E. The dose does not exceed 3 mg/kg every 3 weeks for a total of 4 doses.

Approval duration: 4 months (16 weeks)

III. Continuation of ipilimumab for adjuvant treatment of melanoma, recurrent brain metastases due to melanoma, malignant pleural mesothelioma, or non-small cell lung cancer **meets the definition of medical necessity** when the following criteria are met:

A. The member has demonstrated a beneficial response to therapy (e.g., brain mets are stable, no disease recurrence with adjuvant treatment, no disease progression)

B. The member has been previously approved by Florida Blue or another health plan in the past 2 years, **OR** the member has previously met all indication-specific criteria for coverage

C. The dose does not exceed the following:

a. Adjuvant treatment of melanoma or brain metastasis (single agent use): 10 mg/kg every 12 weeks

b. Malignant Pleural Mesothelioma or Non-small cell lung cancer (in combination with nivolumab): 1 mg/kg every 6 weeks

Approval duration: 1 year

DOSAGE/ADMINISTRATION:

THIS INFORMATION IS PROVIDED FOR INFORMATIONAL PURPOSES ONLY AND SHOULD NOT BE USED AS A SOURCE FOR MAKING PRESCRIBING OR OTHER MEDICAL DETERMINATIONS. PROVIDERS SHOULD REFER TO THE MANUFACTURER'S FULL PRESCRIBING INFORMATION FOR DOSAGE GUIDELINES AND OTHER INFORMATION RELATED TO THIS MEDICATION BEFORE MAKING ANY CLINICAL DECISIONS REGARDING ITS USAGE.

FDA-approved:

- Unresectable or metastatic melanoma: 3 mg/kg administered intravenously (IV) over 90 minutes every three weeks for a total of 4 doses. In the event of toxicity, doses may be delayed, but all treatment must be administered within 16 weeks of the first dose.
- Adjuvant treatment of patients with cutaneous melanoma with regional lymph node involvement of more than 1 mm who have undergone complete resection, including lymphadenectomy: 10 mg/kg administered intravenously (IV) over 90 minutes every three 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. In the event of toxicity, doses are omitted, not delayed.
- Patients with intermediate or poor risk previously untreated advanced renal cell carcinoma in combination with nivolumab: Administer nivolumab 3 mg/kg intravenous infusion over 30 minutes followed by ipilimumab 1 mg/kg infusion over 30 minutes on the same day every 3 weeks for 4 doses, After 4 doses of the combination, nivolumab is given as a single agent as 240 mg every 2 weeks or 480 mg every 4 weeks.
- 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. Administer nivolumab 3 mg/kg intravenous infusion over 30 minutes followed by ipilimumab 1 mg/kg infusion over 30 minutes on the same day every 3 weeks for 4 doses, After 4 doses of the combination, nivolumab is given as a single agent as 240 mg every 2 weeks.

Dose Adjustments/Discontinuation

Although dose adjustments are not required for persons with renal impairment or mild hepatic impairment, ipilimumab has not been evaluated in persons with moderate or severe hepatic impairment.

See prescribing information for recommended treatment modifications for immune-mediated adverse reactions.

Ipilimumab should be discontinued for any of the following:

- Grade 2 adverse reactions lasting 6 weeks or longer (CTCAE)
- Inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day
- Grade 3 or 4 adverse reactions (CTCAE)
- Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy or requires systemic treatment

Drug Availability: ipilimumab is supplied as a 50 mg/10 mL or 200 mg/40 mL single-use vial.

PRECAUTIONS:

Boxed Warning

- Treatment with ipilimumab can result in severe and fatal immune-mediated adverse reactions due to T-cell activation and proliferation. Although the reactions may involve any organ system, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. These may occur initially during treatment or weeks to months following discontinuation.
- Permanently discontinue ipilimumab and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.
- Assess members for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.

Warnings/Precautions

- Immune-mediated adverse reactions: Permanently discontinue for severe reactions. Withhold dose for moderate immune-mediated adverse reactions until return to baseline, improvement to mild severity, or complete resolution, and member is receiving less than 7.5 mg prednisone or equivalent per day. Administer systemic high-dose corticosteroids for severe, persistent, or recurring immune-mediated reactions.
- Immune-mediated hepatitis: Evaluate liver function tests before each dose of ipilimumab
- Immune-mediated endocrinopathies: Monitor ACTH level, thyroid function tests and clinical chemistries prior to each dose. Evaluate at each visit for signs and symptoms of endocrinopathy. Institute hormone replacement therapy as needed.
- Immune-mediated pneumonitis: Permanently discontinue for severe or life-threatening pneumonitis. Withhold dose for moderate immune-mediated adverse reactions.
- Immune-mediated nephritis and renal dysfunction: Permanently discontinue for life-threatening serum creatinine elevation. Withhold dose for moderate to severe immune-mediated adverse reactions.
- Immune-mediated encephalitis: Permanently discontinue for immune-mediated encephalitis. Withhold dose for new onset moderate or severe immune-mediated adverse reactions.
- Infusion reactions: Discontinue for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion for mild or moderate infusion reactions.
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.

BILLING/CODING INFORMATION:

HCPCS Coding:

J9228	Injection, ipilimumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

C17.0 – C17.9	Malignant neoplasm of small intestine
C18.0 – C18.9	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21.8	Malignant neoplasm of overlapping sites of rectum, anus and anal canal
C33	Malignant neoplasm of trachea
C34.00 – C34.02	Malignant neoplasm of unspecified main bronchus
C34.10 – C34.12	Malignant neoplasm of upper lobe, unspecified bronchus or lung
C34.2	Malignant neoplasm of middle lobe, bronchus or lung
C34.30 – C34.32	Malignant neoplasm of lower lobe, unspecified bronchus or lung
C34.80 – C34.82	Malignant neoplasm of overlapping sites of unspecified bronchus and lung
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C38.4	Malignant neoplasm of pleura
C43.0 – C43.9	Malignant melanoma of skin
C45.0	Mesothelioma of pleura
C64.1 – C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1 – C65.9	Malignant neoplasm of unspecified renal pelvis
C69.30 – C69.32	Malignant neoplasm of choroid
C69.40 – C69.42	Malignant neoplasm of ciliary body
C69.60 – C69.62	Malignant neoplasm of orbit
C69.90	Malignant neoplasm of unspecified site of unspecified eye
C69.91	Malignant neoplasm of unspecified site of right eye
C69.92	Malignant neoplasm of unspecified site of left eye
C78.00 - C78.89	Secondary malignant neoplasm of respiratory and digestive organs
C79.31	Secondary malignant neoplasm of brain
C79.51 - C79.52	Secondary malignant neoplasm of bone and bone marrow
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified

REIMBURSEMENT INFORMATION:

Refer to section entitled **POSITION STATEMENT**.

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage products: No National Coverage Determination (NCD) and/or Local Coverage Determination (LCD) were found at the time of the last guideline revised date.

DEFINITIONS:

Table 1: Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

RELATED GUIDELINES:

Adoptive Immunotherapy, 01-96400-01

Autologous Bone Marrow and Stem Cell Transplantation, 02-38241-01

Brachytherapy-Oncologic Applications, 04-77260-20

Carboplatin (Paraplatin®) IV, 09-J0000-96

Dermatoscopy, 02-10000-17

Nivolumab (Opdivo), 09-J2000-33

Paclitaxel and Paclitaxel (protein-bound) IV, 09-J1000-05

Positron Emission Tomography (PET Scans) Oncologic Application, 04-78000-17

Proton Beam Therapy, 04-77260-18

Transpupillary Thermotherapy (TTT), 01-92000-20

Whole Body Photography for Early Detection of Malignant Melanoma, 01-96900-03

OTHER:

Table 2: Common Terminology Criteria for Adverse Events v4.0 (CTCAE)

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated
2	Moderate; minimal, local or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living

4	Life-threatening consequences; urgent intervention indicated
5	Death related to adverse event

TABLE 3: International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Criteria

Prognostic factors	**Notes**
Less than one year from time of diagnosis to systemic therapy	n/a
Karnofsky Performance status <80%	n/a
Hemoglobin < lower limit of normal	Normal: 12 g/dL
Calcium > upper limit of normal	Normal: 8.5 – 10.2 mg/dL
Neutrophil > upper limit of normal	Normal: 2.7 – 7.0 x 109/L
Platelets > upper limit of normal	Normal: 150,000 – 400,000
Prognostic risk groups: **Favorable risk:** no prognostic factors **Intermediate risk:** one or two prognostic factors **Poor-risk:** three to six prognostic factors	

TABLE 4: Karnofsky Performance Status (KPS) (%)

Karnofsky Performance Status (KPS) (%)		
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 04/10/19.

GUIDELINE UPDATE INFORMATION:

08/15/11	New Pharmacy Coverage Guideline.
01/01/12	Revision to guideline; consisting of updating coding.
02/15/12	Revision to guideline; consisting of modifying position statement and updating coding.
08/15/13	Review and revision to guideline consisting of reformatting and revising description section and position statement; reformatting dosage/administration and precautions section; updating position statement and references.
10/15/14	Review and revision to guideline; consisting of revising the position statement, updating references.
09/15/15	Revision to guideline; consisting of position statement, coding
11/15/15	Review and revision to guideline; consisting of revising position statement;, warnings/precautions section, definitions, coding and references.
12/15/15	Revision to guideline; consisting of updating position statement, description and references.
07/15/16	Review and revision to guideline; consisting of revising position statement, description, dosing, warnings, coding, and references.
09/15/16	Revision to guideline; consisting of updating position statement, description, coding and references.
10/15/16	Revision to guideline; consisting of updating position statement, description, dose adjustments, and references.
04/15/17	Revision to guideline; consisting of updating position statement and references.
09/15/16	Review and revision to guideline; consisting of revising position statement, description, coding, and references.
10/15/17	Revision to guideline; consisting of updating position statement and references.
12/15/17	Revision to guideline; consisting of updating position statement and references.
04/15/18	Review and revision to guideline; consisting of revising position statement, description, coding and references.
05/15/18	Revision to guideline; consisting of updating position statement, coding and references.
08/15/18	Revision to guideline; consisting of updating position statement, coding and references.
12/15/18	Revision to guideline; consisting of updating position statement and references.
05/15/19	Review and revision to guideline; consisting of revising position statement, description, coding and references.