**09-J1000-34**

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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, hepatocellular carcinoma, malignant pleural mesothelioma, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer , and non-small cell lung cancer.

Current National Comprehensive Cancer Network (NCCN) guidelines provide recommendations for the use of ipilimumab for ampullary cancer, bone cancer, colorectal cancer, esophageal cancer, hepatocellular carcinoma, kidney cancer, melanoma, mesothelioma, non-small cell lung cancer, small bowel adenocarcinoma, and uveal melanoma.

## POSITION STATEMENT:

**Drug Waste Reduction**: Additional medical necessity criteria for dose optimization may apply depending on the requested dose and member's benefit. Refer to Medical Coverage Guideline Drug Waste Reduction, 09-J5000-54.

**Site of Care**: If ipilimumab (Yervoy) Injection is administered in a hospital-affiliated outpatient setting, additional requirements may apply depending on the member's benefit. Refer to 09-J3000-59, Site of Care Policy for Select Oncology Medications.

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

d. Ipilimumab is used in combination with pembrolizumab as second-line or subsequent therapy if not previously used for disease progression on single agent anti-PD-1 therapy

3. The dose does not exceed **ONE** of the following:

a. 1 mg/kg every 3 weeks for a total of 4 doses when used with nivolumab 3 mg/kg

b. 3 mg/kg every 3 weeks for a total of 4 doses when used with nivolumab 1 mg/kg

c. 3 mg/kg every 3 weeks for a total of 4 doses when used as a single agent

d. 1 mg/kg every 3 weeks for a total of 4 doses when used with pembrolizumab 2 mg/kg

B. Adjuvant or neoadjuvant 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 oligometastatic disease who with no evidence of disease following complete resection, sterotactic ablative therapy or T-VEC/intralesional therapy, or systemic therapy followed by resection

d. Member has resectable or limited resectable stage III disease and ipilimumab will be used in the neoadjuvant setting

e. Member has resectable or limited resectable disease with local satellite/in-transit recurrence or nodal recurrence and ipilimumab will be used in the neoadjuvant setting

2. **ONE** of the following:

a. Ipilimumab will be used as a single agent and the member previously received anti-PD-1 therapy (e.g., nivolumab, pembrolizumab) in the adjuvant setting

b. Ipilimumab will be used in combination with nivolumab

3. The dose does not exceed the following:

a. Single agent: 3 mg/kg every 3 weeks for a total of 4 doses

b. Combination with nivolumab:

i. 3 mg/kg every 3 weeks for a total of 4 doses when used with nivolumab 1 mg/kg

ii. 80 mg every 3 weeks for a total of 2 doses when used with nivolumab 240 mg in the neoadjuvant setting

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

1. Ipilimumab is used as a single agent or in combination with nivolumab

2. The dose does not exceed the following:

a. Single agent use: 3 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. Adrenal tumors when **ALL** of the following are met:

1. Member has locoregional unresectable or metastatic adrenocortical carcinoma

2. Ipilimumab will be used in combination with nivolumab

3. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses

E. Ampullary cancer when **ALL** of the following are met:

1. Member has metastatic, advanced, or unresectable disease

2. Tumor is classified as microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR]

3. The member has not previously received a checkpoint inhibitor

4. Ipilimumab will be used in combination with nivolumab

5. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses

F. Bile duct cancer

1. Member has unresectable, resected gross residual (R2) disease, or metastatic disease

2. Member’s tumor is classified as mutational burden-high (TMB-H) with 10 or more mutations per megabase

3. When used as subsequent therapy after disease progression on initial treatment

4. Ipilimumab will be used in combination with nivolumab

5. The dose does not exceed 1 mg/kg every 6 weeks

G. Bone cancer (includes chondrosarcoma, Ewing sarcoma, osteosarcoma, dedifferentiated chondrosarcoma, chordoma, high-grade undifferentiated pleomorphic sarcoma (UPS) when all of the following are met:

1. Member has unresectable or metastatic disease
2. Member's tumor is classified as mutational burden-high (TMB-H) with 10 or more mutations per megabase
3. When used as subsequent therapy after disease progression on initial treatment
4. Ipilimumab will be used in combination with nivolumab
5. The dose does not exceed 1 mg/kg every 6 weeks

H. Colon or rectal cancer (includes appendiceal adenocarcinoma) when **ALL** of the following are met:

1. Member has metastatic, advanced, unresectable, T4b disease, or medically inoperable disease
2. Tumor is classified as microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR] or POLE/POLD1 mutation with ultra-hypermutated phenotype [TMB greater than 50 mut/mB]
3. Ipilimumab will be used in combination with nivolumab
4. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses

I. Esophageal carcinoma when **ALL** of the following are met:

1. The member has **ONE** of the following:
    1. Member has PD-L1 expression greater than or equal to 1%
    2. Member's tumor is classified as microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR]
2. Ipilimumab will be used in combination with nivolumab
3. The dose does not exceed 1 mg/kg every 6 weeks

J. Gallbladder cancer

1. Member has unresectable, resected gross residual (R2) disease, locoregionally advanced disease, or metastatic disease
2. Member's tumor is classified as mutational burden-high (TMB-H) with 10 or more mutations per megabase
3. When used as subsequent therapy after disease progression on initial treatment
4. Ipilimumab will be used in combination with nivolumab
5. The dose does not exceed 1 mg/kg every 6 weeks

K. Gastric cancer

1. Tumor is classified as microsatellite instability-high [MSI-H] or mismatch repair deficient [dMMR]
2. Ipilimumab will be used in combination with nivolumab
3. The dose does not exceed 1 mg/kg every 6 weeks for 16 weeks

L. Gestational Trophoblastic Neoplasia

1. Member has **ONE** of the following:
    a. High-risk disease
    b. Recurrent or progressive intermediate trophoblastic tumor
2. Ipilimumab will be used in combination with nivolumab
3. The dose does not exceed 1 mg/kg every 6 weeks

M. Head and Neck Cancer
1. Member has unresectable, recurrent, or metastatic non-nasopharyngeal cancer
2. Member has a combined positive score (CPS) greater than or equal to 20
3. Ipilimumab will be used in combination with nivolumab
4. The dose does not exceed 1 mg/kg every 6 weeks

N. Hepatocellular carcinoma when **ALL** of the following are met:
1. **ONE** of the following:
    a. Unresectable disease and is not a candidate for transplant
    b. Metastatic disease
    c. Inoperable due to performance status or comorbidities
2. Member has not previously been treated with ipilimumab or tremelimumab
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

O. Kaposi Sarcoma (Classic type)
1. Member has relapsed or refractory advanced cutaneous, oral, visceral, or nodal disease
2. When used as subsequent therapy after disease progression on initial treatment
3. Ipilimumab will be used in combination with nivolumab
4. The dose does not exceed 1 mg/kg every 6 weeks

P. 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 first-line therapy for member's with intermediate or poor-risk (see Table 3)
    c. 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

Q. Merkel cell carcinoma

1. Ipilimumab will be used as a single agent or in combination with nivolumab
2. The dose does not exceed **ONE** of the following:
    e. 1 mg/kg every 3 weeks for a total of 4 doses
    f. 3 mg/kg every 3 weeks for a total of 4 doses
    g. 1 mg/kg every 6 weeks

R. Mesothelioma (includes malignant pleural mesothelioma, malignant peritoneal mesothelioma, pericardial mesothelioma, and tunica vaginalis testis mesothelioma) when **ALL** of the following are met:
1. **ONE** of the following:
    a. Ipilimumab will be used as first line therapy
    b. Ipilimumab will be used as subsequent therapy if not previously used
2. Ipilimumab will be used in combination with nivolumab
3. The dose does not exceed 1 mg/kg every 6 weeks

S. 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. Recurrent
    c. Advanced
2. **ONE** of the following:
    a. First-line therapy for PD-L1 expression ≥ 1% as detected by an FDA-approved test and EGFR and ALK negative
    b. First line therapy if no ALK rearrangements, RET rearrangements, ROS1 rearrangements, EGFR exon 19 deletion, or EGFR p.L858R point mutation in exon 21
    c. First line therapy if EGFR and ALK are negative
    d. First line therapy for EGFR exon 20 mutation positive tumors
    e. First line therapy for KRAS G12C mutation positive tumors
    f. First line or subsequent therapy if BRAF V600E mutation is positive
    g. First line or subsequent therapy if NTRK1/2/3 gene fusion positive
    h. First line or subsequent therapy for MET exon 14 skipping mutation positive tumors
    i. First line therapy for ERBB2(ERb-B2 Receptor Tyrosine Kinase 2)/HER2 mutation positive tumors
    j. First line therapy for NRG1 gene fusion positive tumors

k. Used as subsequent therapy if not previously used after disease progression with targeted therapy for EGFR S768I, L861Q, and/or G719X mutation positive tumors (e.g., afatinib, osimertinib, erlotinib, gefitinib, dacomitinib)

l. When used as maintenance therapy in combination with nivolumab for members who achieved tumor response or stable disease with previous nivolumab/ipilimumab with or without platinum-doublet chemotherapy

3. Ipilimumab is used in combination with nivolumab*

4. The dose does not exceed 1 mg/kg every 6 weeks

T. Small bowel adenocarcinoma

1. Member has metastatic, unresectable advanced, or medically inoperable disease

2. Member's tumor is classified as microsatellite instability-high [MSI-H], mismatch repair deficient [dMMR], or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [tumor mutational burden (TMB) is greater than 50 mutations per megabase]

3. Ipilimumab will be used in combination with nivolumab

4. The dose does not exceed 1 mg/kg every 3 weeks for a total of 4 doses

U. Soft tissue sarcoma

1. Member has metastatic disease, unresectable advanced disease, or recurrent stage IV disease

2. **ONE** of the following:

a. Member's tumor is classified as mutational burden-high (TMB-H) with 10 or more mutations per megabase

b. When used for one of the following: angiosarcoma, myxofibrosarcoma, undifferentiated pleomorphic sarcoma, dedifferntiated liposarcoma, cutaneous angiosarcoma, undifferentiated sarcomas, well differentiated liposarcoma, atypical lipomatous tumor, pleomorphic rhabdomyosarcoma

3. Member has not previously received treatment with a checkpoint inhibitor

4. Ipilimumab will be used in combination with nivolumab

5. The dose does not exceed 1 mg/kg every 6 weeks

V. 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

W. 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 12 weeks or longer involving any organ system (CTCAE)

2. Inability to reduce corticosteroid to 10 mg prednisone or equivalent per day within 12 weeks of initiation

3. Any Grade 4 or higher immune-mediated reactions involving any organ system (CTCAE)

4. Any recurrent severe Grade 3 or higher immune-mediated reactions requiring systemic immunosuppressive treatment (CTCAE)

5. Any Grade 3 or higher infusion-related reactions (CTCAE)

6. 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 **ONE** of the following:

1. 1 mg/kg every 3 weeks for a total of 4 doses when used with nivolumab 3 mg/kg

2. 3 mg/kg every 3 weeks for a total of 4 doses when used with nivolumab 1 mg/kg

3. 3 mg/kg every 3 weeks for a total of 4 doses when used as a single agent

4. 1 mg/kg every 3 weeks for a total of 4 doses when used with pembrolizumab 2 mg/kg

**Approval duration**: 4 months (16 weeks)

III.Continuation of ipilimumab for adjuvant treatment of melanoma, brain metastases due to melanoma, bile duct cancer, bone cancer, esophageal squamous cell carcinoma, gallbladder cancer, Kaposi sarcoma, Merkel cell carcinoma, mesothelioma, non-small cell lung cancer, or soft tissue sarcoma **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:

1. Adjuvant treatment of melanoma or brain metastasis (single agent use only): 3 mg/kg every 12 weeks

2. Bile duct cancer, bone cancer, esophageal squamous cell adenocarcinoma,gallbladder cancer, gestational trophoblastic neoplasia, head and neck cancer, Kaposi sarcoma, Merkel cell carcinoma, mesothelioma, non-small cell lung cancer, or soft tissue sarcoma (in combination with nivolumab): 1 mg/kg every 6 weeks

**Approval duration:** 1 year

†Includes incomplete resection

*May be combined with or without a platinum and pemetrexed for nonsquamous cell histology or a platinum and paclitaxel for squamous cell histology

## 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 30 minutes every three weeks for a total of 4 doses as a single agent. When combined with nivolumab, 3 mg/kg administered intravenously (IV) over 30 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: 3 mg/kg administered intravenously (IV) over 30 minutes every three weeks for 4 doses followed by 3 mg/kg every 12 weeks for 4 additional doses.
- 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.

- Hepatocellular carcinoma following treatment with sorafenib, in combination with nivolumab: 3 mg/kg administered intravenously (IV) over 30 minutes, immediately following nivolumab administered on the same day, every three weeks for a total of 4 doses or until intolerable toxicity or disease progression as a single agent. 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 adults 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: 1 mg/kg administered intravenously (IV) over 30 minutes every 6 weeks with 360 mg every 3 weeks until disease progression, intolerable toxicity or for up to 2 years in patients without disease progression.
- Treatment of adults with metastatic or recurrent non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations as first-line treatment, in combination with nivolumab and 2 cycles of platinum-doublet chemotherapy: 1 mg/kg administered intravenously (IV) over 30 minutes every 6 weeks with nivolumab 360 mg every 3 weeks and histology-based platinum-doublet chemotherapy every 3 weeks for 2 cycles until disease progression, intolerable toxicity or for up to 2 years in patients without disease progression.
- Treatment of adults with unresectable malignant pleural mesothelioma as first-line treatment, in combination with nivolumab: 1 mg/kg administered intravenously (IV) over 30 minutes every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, intolerable toxicity or for up to 2 years in patients without disease progression.
- Treatment of adult patients with unresectable advanced or metastatic esophageal squamous cell carcinoma, as first line treatment in combination with nivolumab: 1 mg/kg administered intravenously (IV) over 30 minutes every 6 weeks with nivolumab 360 mg every 3 weeks until disease progression, intolerable toxicity or for up to 2 years in patients without disease progression.

**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**

- none

**Warnings/Precautions**

- Immune-mediated adverse reactions: Withhold for severe (grade 3) and permanently discontinue for life-threatening (grade 4) immune-mediated adverse reactions.

  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, endocrinopathy, pneumonitis, and nephritis. Evaluate clinical chemistries including liver function, creatinine, adrenocorticotropic hormone (ACTH) level, and thyroid function tests at baseline and before each dose. See prescribing information for dose modifications of immune-mediated reactions.
- Immune-mediated diarrhea or colitis: immune-mediated diarrhea/colitis may be severe or fatal. Cytomegalovirus(CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated diarrhea/colitis.
- Immune-mediated dermatitis: immune-mediated rash or dermatitis, including bullous and exfoliative dermatitis, Stevens Johnson Syndrome and toxic epidermal necrolysis (TEN), may be severe or fatal. Topical emollients and/or topical corticosteroids may be adequate for mild or moderate non-bullous/exfoliative rashes. Withhold or permanently discontinue depending on the severity.
- Immune-mediated hepatitis: Evaluate liver function tests before each dose of ipilimumab. Withhold for moderate and permanently discontinue for severe or life-threatening transaminase or total bilirubin elevation.
- 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 and monitor changes in renal function.
- Immune-mediated encephalitis: Permanently discontinue for immune-mediated encephalitis. Withhold dose for new onset moderate or severe neurological signs or symptoms.
- Infusion reactions: Discontinue for severe and life-threatening infusion reactions. Interrupt or slow the rate of infusion for mild or moderate infusion reactions.
- Complications of allogenic hematopoietic stem cell transplant: Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive ipilimumab before or after allogeneic hematopoietic stem cell transplantation (HSCT). See prescribing information for more information.
- Embryo-fetal toxicity: Can cause fetal harm. Advise of potential risk to a fetus and use of effective contraception.
- Risks associated with use in combination with nivolumab: additional risks apply to combination use with nivolumab. See prescribing information for more information.

## BILLING/CODING INFORMATION:

### HCPCS Coding:

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| J9228 | Injection, ipilimumab, 1 mg |

## ICD-10 Diagnosis Codes That Support Medical Necessity:

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| C00.0 – C08.9 | Malignant neoplasm of lip, base of tongue, of other and unspecified parts of tongue, gum, floor of mouth, palate, of other and unspecified parts of mouth, parotid and salivary gland. |
| C09.0 – C10.9 | Malignant neoplasm of tonsil and oropharynx |
| C12.0 – C14.8 | Malignant neoplasm of piriform sinus, hypopharynx and other and ill-defined sites in the lip, oral cavity and pharynx. |
| C15.3 – C15.9 | Malignant neoplasm of esophagus |
| C16.0 – C16.9 | Malignant neoplasm of cardia |
| 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 |
| C22.0 | Liver cell carcinoma |
| C22.1 | Intrahepatic bile duct carcinoma |
| C22.2 | Hepatoblastoma |
| C22.3 | Angiosarcoma of liver |
| C22.7 | Other specified carcinomas of liver |
| C22.8 | Malignant neoplasm of liver, primary, unspecified as to type |
| C22.9 | Malignant neoplasm of liver, not specified as primary or secondary |
| C23 | Malignant neoplasm of gallbladder |
| C24.0 – C24.9 | Malignant neoplasm of other and unspecified parts of biliary tract |
| C31.0 - C31.1 | Malignant neoplasm of accessory sinuses |
| C32.0 – C32.9 | Malignant neoplasm of larynx |
| 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 |
| C40.00 – C40.92 | Malignant neoplasm of bone and articular cartilage of limbs |
| C41.0 – C41.9 | Malignant neoplasm of bone and articular cartilage of other and unspecified sites |
| C43.0 – C43.9 | Malignant melanoma of skin |
| C44.00 – C44.09 | Malignant neoplasm of skin |
| C45.0 – C45.9 | Mesothelioma of pleura, peritoneum, pericardium, and other sites |
| C47.0 – C 47.9 | Malignant neoplasm of peripheral nerves and autonomic nervous system |
| C48.0 – C48.8 | Malignant neoplasm of retroperitoneum and peritoneum |
| C49.0 – C49.9 | Malignant neoplasm of other connective and soft tissue |
| C4A.0 – C4A.9 | Merkel cell carcinoma, unspecified |
| C58 | Malignant neoplasm of placenta |
| 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 |
| C72.0 – C72.1 | Malignant neoplasm of spinal cord and cauda equina |
| C74.00-C74.92 | Malignant neoplasm of cortex of unspecified adrenal gland |

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|---|---|
| C76.0 | Malignant neoplasm of head, face and neck |
| C77.0 | Secondary and unspecified malignant neoplasm of lymph nodes of head, face and neck |
| 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 |
| C79.70 – C79.72 | Secondary malignant neoplasm of unspecified adrenal gland |
| C7A.8 | Other malignant neuroendocrine tumors |
| C7B.1 | Secondary Merkel cell carcinoma |
| C7B.00-C7B.8 | Secondary carcinoid tumors, unspecified |
| C80.0 | Disseminated malignant neoplasm, unspecified |
| C80.1 | Malignant (primary) neoplasm, unspecified |
| D37.01 – D37.09 | Neoplasm of uncertain behavior of lip, tongue, salivary glands, pharynx, and other sites of the oral cavity |
| D37.1 | Neoplasm of uncertain behavior of stomach |
| D37.8 | Neoplasm of uncertain behavior of other specified digestive organs |
| D37.9 | Neoplasm of uncertain behavior of digestive organ, unspecified |
| D38.0 – D38.6 | Neoplasm of uncertain behavior of larynx, trachea, bronchus, thymus, and other respiratory organs |
| D39.2 -D39.9 | Neoplasm of uncertain behavior of placenta, other female genital organs |
| O01.9 | Hydatidiform mole, 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.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

## 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:**<br>**Favorable risk:** no prognostic factors<br>**Intermediate risk:** one or two prognostic factors<br>**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 | 70 | Cares for self; unable to carry on normal activity or to do active work. |

| | | |
|---|---|---|
| home and care for most personal needs; varying amount of assistance needed. | 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 |

### TABLE 5: Child-Pugh Score and Classification

| | 1 point | 2 points | 3 points |
|---|---|---|---|
| Total bilirubin | < 2 | 2-3 | > 3 |
| Serum albumin | > 3.5 | 2.8-3.5 | < 2.8 |
| INR | > 1.7 | 1.71-2.20 | < 2.20 |
| Ascites | None | Mild | Severe |
| Hepatic encephalopathy | None | Grade I-II | Grade III-IV |
| **Classification of Result:**<br>Class A: 5-6 points<br>Class B: 7-9 points<br>Class C: 10-15 points | | | |

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## COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 03/12/25.

## 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. |
| 08/15/19 | Revision to guideline; consisting of updating position statement and references. |
| 02/15/20 | Revision to guideline; consisting of updating the position statement and references. |
| 05/15/20 | Review and revision to guideline; consisting of updating the position statement , description, dosing , warnings, and references. |
| 06/15/20 | Revision to guideline; consisting of updating the position statement. |
| 07/15/20 | Revision to guideline; consisting of updating the position statement, description, dosing, and references. |

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| 11/15/20 | Revision to guideline; consisting of updating the position statement, description, dosing, and references. |
| 01/15/21 | Revision to guideline; consisting of updating the position statement and references. |
| 03/15/21 | Revision to guideline; consisting of updating the position statement and references. |
| 12/15/21 | Revision to guideline; consisting of updating the position statement and references. |
| 07/15/22 | Revision to guideline; consisting of updating the position statement and references. |
| 02/15/23 | Revision to guideline; consisting of adding bone cancer to the policy and updating the use for adjuvant treatment of melanoma, colon cancer, and non-small cell lung cancer. Updates to description, dosing, coding and references. |
| 01/15/24 | Revision to guideline; consisting of adding bile cancer, gallbladder cancer, gastric cancer, Kaposi sarcoma, merkel cell carcinoma, and soft tissue sarcoma to the policy and updating the use for adjuvant treatment of melanoma, colon cancer, and esophageal cancer. Updates to dosing, coding, and references. |
| 04/15/25 | Review and revision to guideline; consisting of updating the position statement for ampullary, bone, bile duct, brain metatases, colorectal, esophageal cancer, gallbladder cancer, hepatocellular cancer, melanoma, merkel cell carcinoma, small bowel adenocarcinoma, non-small cell lung cancer, soft tissue sarcoma. Added gestational trophoblastic neoplasia and head and neck cancer to the position statement. |
| 07/15/25 | Revision to guideline; consisting of adding Adrenal tumors and updating colon, esophageal, and hepatocellular cancer. |
| 06/01/26 | Revision: Added Drug Waste Reduction statement to the Position Statement. |
| 07/01/26 | Revision: Added Site of Care statement to the Position Statement. |