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Subject: Nivolumab (Opdivo®)

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DESCRIPTION:

Nivolumab (Opdivo) is a monoclonal antibody that enhances the antitumor response by binding to the programmed death receptor-1 (PD-1) and blocking its interaction with ligand 1 and 2 (PD-L1 and PD-L2). It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of patients with unresectable or metastatic melanoma, microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, non-small cell lung cancer (NSCLC), and advanced renal cell carcinoma as a single agent or in combination with ipilimumab. It has also been approved in combination with cabozantinib for advanced renal cell carcinoma. Nivolumab is also FDA-approved for NSCLC in combination with ipilimumab combined with 2 cycles of platinum-doublet chemotherapy, and for malignant pleural mesothelioma and hepatocellular cancer in combination with ipilimumab. Nivolumab is FDA-approved as a single agent for the treatment of Classical Hodgkin lymphoma that has relapsed or progressed, recurrent or metastatic squamous cell carcinoma of the head and neck, urothelial carcinoma, esophageal squamous cell carcinoma, and for the adjuvant treatment of melanoma. Most recently, nivolumab was approved for the treatment of gastric cancer, gastroesophageal junction cancer, and esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy. Certain indications are approved under accelerated approval based on tumor response rate and durability of response (i.e., CHL, urothelial carcinoma, colorectal cancer, and hepatocellular carcinoma). Continued approval for these indications may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The initial safety and efficacy of nivolumab were evaluated in a randomized, open-label phase 3 trial (CheckMate-37) of subjects with unresectable (Stage IIIc) or metastatic (Stage IV) melanoma and disease progression following ipilimumab and, if BRAF V600 mutation–positive, a BRAF inhibitor. Subjects were randomized to receive nivolumab 3 mg/kg every 2 weeks (n=268) or investigator's choice of chemotherapy (n=102), either dacarbazine or carboplatin plus paclitaxel. The primary endpoints were

objective response rate (ORR) and overall survival. Efficacy was assessed in a single-arm, noncomparative, preplanned interim analysis in the first 120 patients who received nivolumab in Trial 1 and in whom the minimum duration of follow-up was six months.

At six months, the primary endpoint of ORR in the 120 patients who received nivolumab was 32% (4 complete and 34 partial responses) with 87% having a response duration of 2.6 to more than 10 months. The ORR included patients with and without BRAF V600 mutation-positive disease. Evidence of a clinical benefit outside of tumor response rate has not been established. The median duration of exposure was 5.3 months (range, 1 day to 13.8+ months), with a median of 8 doses (range, 1-31) in nivolumab-treated patients, and was 2 months (range, 1 day to 9.6+ months) in chemotherapy-treated patients. In this ongoing trial, 24% of patients received nivolumab for more than 6 months and 3% of patients received nivolumab for more than 1 year.

Nivolumab was discontinued for adverse reactions in 9% of patients, while 26% of patients receiving nivolumab had a drug delay for an adverse reaction. The most common adverse reaction (reported in at least 20% of patients) was rash.

National Comprehensive Cancer Network (NCCN) Guidelines include recommendations for use of nivolumab for the treatment of various types of cancer.

POSITION STATEMENT:

Initiation of nivolumab (Opdivo) **meets the definition of medical necessity** for members when **ALL** of the following are met:

I. **ONE** of the following to support clinical use is met:

A. **ALL** of the following are met regarding FDA labeling or NCCN Compendium:

i. **ONE** of the following (indication and usage):

1. 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)

2. Indication is recognized in NCCN Drugs and Biologics Compendium **AND** usage as a Category 1 or 2A recommendation (Table 1).

ii. **ONE** of the following (diagnostic testing¶):

1. **ALL** of the following:

a. The requested indication requires genetic/specific diagnostic testing per FDA labeling or NCCN Compendium for the requested agent

b. Genetic/specific diagnostic testing has been completed

c. The results of the genetic/specific diagnostic testing indicate therapy with the requested agent is appropriate.

2. The requested indication does **NOT** require specific genetic/diagnostic testing per FDA labeling or NCCN Compendium.

B. Requested product is designated as an orphan drug by the FDA for the requested indication **AND** the indication is not included in the FDA labeling or the NCCN compendium as a 1 or 2A recommendation (i.e., "Designated/Approved", "Designated") (Orphan drug designations can be found at http://www.accessdata.fda.gov/scripts/opdlisting/oopd/)

C. The indication **AND** usage of the requested product is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article.

NOTE:

- Case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support for use.
- Clinical studies must be supportive of use for a similar patient population (e.g., indication, diagnosis, disease severity, genetic or tumor mutations) and for the intended treatment plan, including any concomitant therapy.

II. Nivolumab will be used as monotherapy with the following exceptions:

A. Combination therapy for the indication is supported by FDA labeling, NCCN Compendium, or standard reference compendia (Table 2)

B. Combination therapy for the indication is supported by the results of TWO or more published clinical studies – prescriber must submit full text copies of each article

i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

III. The dose does not exceed the maximum FDA-approved dose and frequency* with the following exceptions:

A. Dose and frequency for indication are supported by NCCN Compendium or standard reference compendia (Table 2)

B. Dose and frequency for indication are supported by the results of TWO or more published clinical studies – prescriber must submit full text copies of each article

NOTE: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

Approval duration: 6 months

Continuation of nivolumab (Opdivo) **meets the definition of medical necessity** for members meeting **ALL** of the following criteria:

1. 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
2. Member's disease has not progressed during treatment with nivolumab
3. Nivolumab will be used as monotherapy with the following exceptions:
    a. Combination therapy for the indication is supported by FDA labeling, NCCN Compendium, or standard reference compendia (Table 2)
    b. Combination therapy for indication is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article

i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

4. The dose does not exceed the maximum FDA-approved dose and frequency with the following exceptions:
    a. Dose and frequency for the indication is supported by NCCN Compendium or standard reference compendia (Table 2)
    b. Dose and frequency for indication is supported by the results of **TWO** or more published clinical studies – prescriber must submit full text copies of each article
        i. **NOTE**: Dose ranging studies, case reports, posters, and abstracts (including published meeting abstracts) are not accepted as evidence to support use

Approval duration: 1 year**

***NOTE**: The maximum FDA approved dose includes the following:

- Single agent:
    - 240 mg every 2 weeks or 480 mg every 4 weeks for adults or pediatric patients age 12 years and older weighing 40 kg or more
    - 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks for pediatric patients age 12 years and older weighing less than 40 kg
- In combination with ipilimumab:
    - 1 mg/kg or 3 mg/kg every 3 weeks for 4 doses, then single agent use with one of the following:
        - 240 mg every 2 weeks or 480 mg every 4 weeks for adults or pediatric patients age 12 years and older weighing 40 kg or more
        - 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks for pediatric patients age 12 years and older weighing less than 40 kg
    - 3 mg/kg every 2 weeks
    - 360 mg every 3 weeks
    - 360 mg every 3 weeks and 2 cycles of platinum-doublet chemotherapy
- In combination with cabozantinib: 240 mg every 2 weeks or 480 mg every 4 weeks
- In combination with chemotherapy: 240 mg every 2 weeks, 360 mg every 3 weeks, or 480 mg every 4 weeks
- Adjuvant treatment of bladder cancer: 240 mg every 2 weeks or 480 mg every 4 weeks up to 1 year in the absence of disease progression or unacceptable toxicity
- Adjuvant treatment of resected esophageal or gastroesophageal junction cancer: 240 mg every 2 weeks or 480 mg every 4 weeks up to 1 year in the absence of disease progression or unacceptable toxicity

- Adjuvant treatment of melanoma in adults or pediatric patients 12 years or older weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks up to 1 year in the absence of disease progression or unacceptable toxicity
- Adjuvant treatment of melanoma in pediatric patients 12 years or older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg ever 4 weeks up to 1 year in the absence of disease progression or unacceptable toxicity
- Neoadjuvant treatment of resectable NSCLC: 360 mg with platinum-doublet chemotherapy on the same day every 3 weeks for 3 cycles

**For adjuvant treatment of melanoma, adjuvant treatment of bladder cancer, or adjuvant treatment of resected esophageal or gastroesophageal junction cancer the duration of therapy is 12 months. For neoadjuvant treatment of NSCLC, the duration of therapy is every 3 weeks for 3 cycles in combination with chemotherapy

† Includes incomplete resection.

¶FDA Companion Diagnostics: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools

Table 1

NCCN Categories of Evidence 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 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

Table 2

Other compendia	
Compendium	**Covered Uses†**
AHFS-DI	Narrative text is supportive
Clinical Pharmacology	Narrative text is supportive
Lexicomp	Evidence rating A, B or G
Thomson Micromedex DrugDex	Meets requirements for **BOTH** of the following: • Strength of recommendation: Class I (Recommended) or IIa (Recommended, In Most Cases) • Efficacy: Class I (Effective) or IIa (Evidence Favors Efficacy)
†If covered use criteria are not met, the request should be denied. AHFS-DI, American Hospital Formulary Service Drug Information; For additional information regarding designated compendia, please refer to the "Definitions" section.	

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

- Single agent use in adults and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks
- Single agent use in pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks
- In combination with ipilimumab: Administer nivolumab 1 mg/kg as an intravenous infusion over 30 minutes, followed by ipilimumab 3 mg/kg infusion over 90 minutes on the same day, every 3 weeks for 4 doses. The subsequent dose of nivolumab is given as a single agent as one of the following:
    - Adults and pediatric patients age 12 years and older and weighing 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks.
    - Pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks

Adjuvant treatment of melanoma with completely resected Stage IIB, Stage IIC, Stage III, or Stage IV melanoma:

- Single agent use in adults and pediatric patients age 12 years and older and weighing 40 kg or more:**:** 240 mg every 2 weeks or 480 mg every 4 weeks up to 1 year.
- Single agent use in pediatric patients age 12 years and older and weighing less than 40 kg: 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks up to 1 year.

Non-small cell lung cancer

Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks

Metastatic non-small cell lung cancer expressing PD-L1 (≥1%)

- In combination with ipilimumab: 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks

Metastatic or recurrent non-small cell lung cancer as first line treatment

- In combination with ipilimumab and 2 cycles of histology-based platinum-doublet chemotherapy: 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of histology-based platinum doublet chemotherapy every 3 weeks

Neoadjuvant use in adult patients with resectable tumors greater than or equal to 4 cm or node positive

- 360 mg with platinum doublet chemotherapy on the same day every 3 weeks for 3 cycles

Advanced renal cell carcinoma

- Single agent if previous use of antiangiogenic therapy: 240 mg every 2 weeks or 480 mg every 4 weeks
- Previously untreated patients with intermediate or poor risk advanced renal cell carcinoma in combination with ipilimumab: 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, The subsequent dose of nivolumab is given as a single agent as 240 mg every 2 weeks or 480 mg every 4 weeks.
- In combination with cabozantinib as first line therapy: 240 mg every 2 weeks or 480 mg every 4 weeks in combination with cabozantinib 40 mg orally once daily without food

Classical Hodgkin Lymphoma:

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks

Recurrent or metastatic squamous cell carcinoma of the head and neck

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks

Urothelial carcinoma

Adjuvant treatment of urothelial carcinoma

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks for up to one year

Locally advanced or metastatic urothelial carcinoma

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks

Unresectable or metastatic urothelial carcinoma

- In combination with cisplatin and gemcitabine: 360 mg every 3 weeks in combination with cisplatin and gemcitabine on the same day every 3 weeks for up to 6 cycles. After completing up to 6 cycles of combination therapy, administer as a single agent as 240 mg every 2 weeks or 480 mg every 4 weeks

Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer

- Single agent use in adults or pediatric patients 12 years of age and older and 40 kg or more: 240 mg every 2 weeks or 480 mg every 4 weeks
- Single agent use in pediatric patients 12 years of age and older and less than 40 kg: 3 mg/kg every 2 weeks
- In combination with ipilimumab: Administer nivolumab 3 mg/kg as an 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. The subsequent dose of nivolumab is given as a single agent in adults or pediatric patients 12 years of age and older and 40 kg or more is 240 mg every 2

weeks or 480 mg every 4 weeks. The subsequent dose of nivolumab in pediatric patients 12 years of age and older and less than 40 kg is 3 mg/kg every 2 weeks

Hepatocellular carcinoma

- In combination with ipilimumab: Administer nivolumab 1 mg/kg as an intravenous infusion over 30 minutes, followed by ipilimumab 3 mg/kg infusion over 30 minutes on the same day, every 3 weeks for 4 doses. The subsequent dose of nivolumab is given as a single agent as 240 mg every 2 weeks or 480 mg every 4 weeks.

Malignant pleural mesothelioma

- In combination with ipilimumab: 360 mg every 3 weeks with ipilimumab 1 mg/kg every 6 weeks

Adjuvant treatment of resected esophageal or gastroesophageal junction cancer

- Single agent use: 240 mg every 2 weeks or 480 mg every 4 weeks for a total treatment duration of 1 year.
- Administer as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity for a total treatment of 1 year.

Gastric cancer, gastroesphageal junction cancer, and esophageal adenocarcinoma

- In combination with fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 360 mg every 3 weeks
- Administer as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity, or up to 2 years.

Esophageal squamous cell carcinoma

- As a single agent: 240 mg every 2 weeks or 480 mg every 4 weeks
- In combination with fluoropyrimidine- and platinum-containing chemotherapy: 240 mg every 2 weeks or 480 mg every 4 weeks
- In combination with ipilimumab: 3 mg/kg every 2 weeks or 360 mg every 3 weeks
- Administer as an intravenous infusion over 30 minutes until disease progression or unacceptable toxicity, or up to 2 years

Note: For members ≤ 67 kg, a dose of 3 mg/kg every 2 weeks may be used. This information is not meant to replace clinical decision making when initiating or modifying medication therapy and should only be used as a guide. Patient-specific variables should be taken into account.

Dose Adjustments

- Refer to prescribing information

Drug Availability

- Injection: 40 mg/4 mL,100 mg/10 mL, and 240 mg/24 mL solution in a single-use vial

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- None

Precautions/Warnings

Immune-mediated adverse reactions: See prescribing information for dose modifications and monitoring recommendations for immune-mediated reactions including: pneumonitis, colitis, hepatitis, endocrinopathies (hypophysitis, adrenal insufficiency, thyroid disorders, hyperglycemia),encephalitis, severe or life-threatening rash, nephritis, renal dysfunction, and infusion reactions.

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 allogeneic HSCT: Monitor for hyperacute graft-versus-host-disease (GVHD), grade 3-4 acute GVHD, steroid-requiring febrile syndrome, hepatic veno-occlusive disease, and other immune-mediated adverse reactions. Transplant-related mortality has occurred.

Embryofetal toxicity: can cause fetal harm. Advise of potential risk to fetus and use of effective contraception.

Treatment of patients with multiple myeloma with a PD-1 or PD-L1 blocking antibody in combination with a thalidomide analogue plus desamethasone is not recommended outside of controlled clinical trials

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding:

J9299	Injection, nivolumab, 1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity:

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
C11.0 – C11.9	Malignant neoplasm of nasopharynx
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 stomach

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
C21.0 – 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
C30.0	Malignant neoplasm of nasal cavity
C31.0 – C31.9	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	Malignant neoplasm of skin of lip
C44.02	Squamous cell carcinoma of skin of lip
C44.09	Other specified malignant neoplasm of skin of lip
C4A.0 – C4A.9	Merkel cell carcinoma
C45.0 – C45.9	Mesothelioma of pleura, peritoneum, pericardium, and other sites
C46.0 – C46.9	Kaposi's sarcoma
C47.0 – C47.9	Malignant neoplasm of peripheral nerves and autonomic nervous system
C48.0 – C48.9	Malignant neoplasm of retroperitoneum and peritoneum
C49.0 – C49.9	Malignant neoplasm of other connective and soft tissue
C51.0 – C51.9	Malignant neoplasm of vulva
C52	Malignant neoplasm of vagina
C53.0 – C53.9	Malignant neoplasm of cervix uteri
C54.0 – C54.9	Malignant neoplasm of corpus uteri
C55	Malignant neoplasm of uterus, part unspecified

C58	Malignant neoplasm of placenta
C61	Malignant neoplasm of prostate (urothelial carcinoma)
C64.1 – C64.9	Malignant neoplasm of unspecified kidney, except renal pelvis
C65.1 – C65.9	Malignant neoplasm of unspecified renal pelvis
C66.1 – C66.9	Malignant neoplasm of ureter
C67.0 – C67.9	Malignant neoplasm of bladder
C68.0 – C68.9	Malignant neoplasm of other and unspecified urinary organs
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
C71.0 – C71.9	Malignant neoplasm of brain
C73	Malignant neoplasm of thyroid gland
C72.0 – C72.9	Malignant neoplasm of spinal cord and cauda equina
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
C7A.1	Malignant poorly-differentiated neuroendocrine tumors
C80.0	Disseminated malignant neoplasm, unspecified
C80.1	Malignant (primary) neoplasm, unspecified
C81.10 – C81.99	Hodgkin Lymphoma
C84.Z0 – C84.Z9	Other mature T/NK-cell lymphomas
C84.90 – C84.99	Mature T/NK-cell lymphomas, unspecified
C85.20 – C85.29	Mediastinal (thymic) large B-cell lymphoma
C86.00	Extranodal NK/T-cell lymphoma, nasal type
C7B.1	Secondary Merkel cell carcinoma
D09.0	Carcinoma in situ of bladder
D19.1	Benign neoplasm of mesothelial tissue of peritoneum
D37.01	Neoplasm of uncertain behavior of lip
D37.02	Neoplasm of uncertain behavior of tongue
D37.04	Neoplasm of uncertain behavior of the minor salivary glands
D37.05	Neoplasm of uncertain behavior of pharynx
D37.09	Neoplasm of uncertain behavior of other specified 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	Neoplasm of uncertain behavior of larynx
D38.5	Neoplasm of uncertain behavior of other respiratory organs

D38.6	Neoplasm of uncertain behavior of respiratory organ, unspecified
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 Part D: Florida Blue has delegated to Prime Therapeutics authority to make coverage determinations for the Medicare Part D services referenced in this guideline.

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

DEFINITIONS:

Table 3: 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:

Dabrafenib (Tafinlar®) Capsules, 09-J2000-00

Ipilimumab (Yervoy®) Injection, 09-J1000-34

Pembrolizumab (Keytruda®) Injection, 09-J2000-22

Trametinib (Mekinist™) Tablets, 09-J1000-99

OTHER:

TABLE 4: 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: Class A: 5-6 points Class B: 7-9 points Class C: 10-15 points			

TABLE 5: 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 10^9/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 6: 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	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.

institutional or hospital care; disease may be progressing rapidly.	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 01/10/24.

GUIDELINE UPDATE INFORMATION:

04/15/15	New Medical Coverage Guideline.
06/15/15	Revision of guideline; consisting of updating description and position statement and references.
07/1/15	Revision of guideline; consisting of coding update.
08/15/15	Revision of guideline; consisting of position statement, coding.

11/15/15	Revision of guideline; consisting of updating position statement, description, dosing/administration, warnings, and references.
12/15/15	Revision to guideline; consisting of updating position statement, description, and references.
01/01/16	Annual HCPCS coding update: added code J9299 and deleted codes C9453 and J9999.
01/15/16	Revision to guideline; consisting of updating position statement, description, precautions, coding and references.
04/15/16	Review and revision to guidelines; updating position statement, references.
6/15/16	Revision to guideline; consisting of updating position statement, description, coding and references.
7/15/16	ICD-10 coding update.
8/15/16	Revision to guideline; consisting of updating position statement and references.
9/15/16	Revision to guideline; consisting of updating position statement, coding and references.
10/15/16	Revision to guideline; consisting of updating position statement, description, precautions, coding and references.
11/15/16	Revision to guideline; consisting of updating position statement, dosing, coding and references.
02/15/17	Review and revision to guideline; updating position statement, description, dosing, coding, and references.
04/15/17	Review and revision to guideline; consisting of updating position statement, description, dosing, coding, and references.
09/15/17	Revision to guideline; consisting of updating position statement, description, coding, and references.
10/15/17	Revision to guideline; consisting of updating position statement, description, coding, and references.
11/15/17	Revision to guideline; consisting of updating position statement, description, coding, and references.
12/15/17	Revision to guideline; consisting of updating position statement and references.
03/15/18	Revision to guideline; consisting of updating position statement, coding and references.
04/15/18	Review and revision to guideline; consisting of updating position statement, dosing, coding, and references.
05/15/18	Revision to guideline; consisting of updating position statement, coding and references.
06/15/18	Revision to guideline; consisting of updating position statement and references.
07/15/18	Update to coding.
08/15/18	Revision to guideline; consisting of updating position statement and references.
10/15/18	Revision to guideline; consisting of updating position statement, dosage/administration, and references.
12/15/18	Revision to guideline; consisting of updating position statement, description, coding and references.
05/15/19	Review and revision to guideline; consisting of updating position statement, description, coding and references.
08/15/19	Revision to guideline; consisting of updating position statement , dosing and references.

02/15/20	Revision to guideline; consisting of updating the position statement, coding and references.
05/15/20	Revision to guideline; consisting of updating the position statement, description, dosing 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.
11/15/20	Revision to guideline; consisting of updating the position statement, description, dosing and references.
03/15/21	Revision to guideline; consisting of updating the position statement, description, dosing and references.
08/15/21	Review and revision to guideline; consisting of updating the position statement, description, dosing, coding, and references.
10/15/21	Revision to guideline; consisting of updating the position statement, description, dosing, and references.
12/15/21	Revision to guideline; consisting of updating the position statement and references.
04/15/22	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	Review and revision to guideline; consisting of updating the position statement, dosing, coding, and references.
02/15/24	Review and revision to guideline; consisting of updating dosing, coding, and references.
10/1/24	ICD-10 coding, dosing, and reference updates.