09-J4000-23

Original Effective Date: 06/15/22

Reviewed: 05/08/24

Revised: 06/15/24

Subject: Nivolumab; Relatlimab-rmbw (Opdualag) injection

THIS MEDICAL COVERAGE GUIDELINE IS NOT AN AUTHORIZATION, CERTIFICATION, EXPLANATION OF BENEFITS, OR A GUARANTEE OF PAYMENT, NOR DOES IT SUBSTITUTE FOR OR CONSTITUTE MEDICAL ADVICE. ALL MEDICAL DECISIONS ARE SOLELY THE RESPONSIBILITY OF THE PATIENT AND PHYSICIAN. BENEFITS ARE DETERMINED BY THE GROUP CONTRACT, MEMBER BENEFIT BOOKLET, AND/OR INDIVIDUAL SUBSCRIBER CERTIFICATE IN EFFECT AT THE TIME SERVICES WERE RENDERED. THIS MEDICAL COVERAGE GUIDELINE APPLIES TO ALL LINES OF BUSINESS UNLESS OTHERWISE NOTED IN THE PROGRAM EXCEPTIONS SECTION.

DESCRIPTION:

Nivolumab is a monoclonal antibody that enhances the antitumor immune 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). Relatlimab is a monoclonal antibody that binds to the lymphocyte activation gene-3 (LAG-3) receptor which results in promoting T cell proliferation and cytokine secretion. The combined agents result in inhibition of tumor growth. Nivolumab;relatlimab-rmbw (Opdualag) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of adult and pediatric patients 12 years and older with unresectable or metastatic melanoma.

The initial safety and efficacy of nivolumab;relatlimab-rmbw (Opdualag) was evaluated in a randomized trial as compared to nivolumab alone in 714 patients with previously untreated unresectable or metastatic Stage III or IV melanoma. Patients were permitted to have received prior adjuvant or neoadjuvant melanoma therapy with anti-PD-1, anti-CTLA-4, or BRAF-MEK inhibitors if received at least 6 months between the last dose of therapy and the date of recurrence. Patients with active autoimmune disease, conditions requiring corticosteroids or immunosuppressive medications, uveal melanoma, and active or untreated brain or leptomeningeal metastases were excluded. Patients received either nivolumab;relatlimab-rmbw or nivolumab every 4 weeks until disease progression or unacceptable toxicity. There were 41% of patients with PD-L1 expression greater than or equal to 1%, 75% of patients with LAG-3 expression greater than or equal to 1%, and 39% with BRAF V600 mutation-positive melanoma. The efficacy outcome measures were progression-free survival (PFS), overall survival (OS) and overall response rate (ORR). There was a significant improvement in PFS with the combination arm as compared to nivolumab alone (10.1 months vs 4.6 months,p= 0.0055). The overall survival was not significant at the time of the analysis (34.2 months vs 25.2 months) and the overall response rate was 43% for the combined group as compared to 33% with nivolumab alone. The most common adverse reactions that occurred in patients treated with nivolumab;relatlimab-rmbw included

musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%). Other clinically relevant reactions that occurred in less than 15% of patients included vitiligo, adrenal insufficiency, myocarditis, and hepatitis. The most common lab abnormalities were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).

National Comprehensive Cancer Network (NCCN) Guidelines for Melanoma include recommendations for the use of nivolumab;relatlimab-rmbw for metastatic or unresectable disease. Metastatic disease includes stage III unresectable/borderline resectable disease with clinically positive node(s) or clinical satellite/in-transit metastases, unresectable local satellite/in-transit recurrence, unresectable nodal recurrence, and widely disseminated distant metastatic disease.

POSITION STATEMENT:

I. Initiation of treatment with nivolumab;relatlimab-rmbw (Opdualag) meets the definition of **medical necessity** when used to treat **ONE** of the following:
   A. Unresectable[†] or metastatic melanoma when **ALL** of the following are met:
      1. Nivolumab;relatlimab-rmbw will be used for **ONE** of the following:
         a. First-line systemic therapy
         b. Second-line or subsequent therapy for disease progression
         c. Reinduction therapy and BOTH of the following:
            i. Members disease relapsed or progressed greater than 3 months after initial clinical response or stable disease with previous nivolumab treatment
            ii. Member does not have any remaining toxicity from previous nivolumab-relatlimab treatment
      2. Nivolumab;relatlimab-rmbw (Opdualag) will be used as a single agent
      3. The dose does not exceed 480 mg nivolumab and 160 mg relatlimab every 4 weeks
   B. Neoadjuvant treatment of melanoma
      1. Used for **ONE** of the following
         a. Stage III clinically positive, resectable nodal disease
         b. Limited resectable stage III disease with clinical satellite/in-transit metastases
         c. Limited resectable local satellite/in-transit recurrence
         d. Resectable disease limited to nodal recurrence
      2. Nivolumab;relatlimab-rmbw (Opdualag) will be used as a single agent
      3. The dose does not exceed 480 mg nivolumab and 160 mg relatlimab every 4 weeks
   C. Other FDA-approved or NCCN-supported diagnosis (not previously listed)
      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. Dose does not exceed the maximum FDA-approved dosing.

Approval duration: 6 months

II. Continuation of nivolumab;relatlimab-rmbw (Opdualag) for the treatment of melanoma or other FDA-approved or NCCN supported diagnosis **meets the definition of medical necessity** when the following criteria are met:

a. The member has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of melanoma or other FDA-approved or NCCN supported diagnosis, **OR** the member has previously met all indication-specific criteria for coverage

b. The member's disease has not progressed while receiving treatment with nivolumab;relatlimab-rmbw (Opdualag)

c. Nivolumab;relatlimab-rmbw (Opdualag) will be used as a single agent

d. The dose does not exceed 480 mg nivolumab and 160 mg relatlimab every 4 weeks.

Approval duration: 1 year

† Includes incomplete resection.

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

- Adults and pediatric patients 12 years of age or older who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab administered every 4 weeks until disease progression or unacceptable toxicity occurs

Dose Adjustments

- See prescribing information for dose modifications for adverse reactions.
- Withhold for severe (grade 3) immune-mediated adverse reactions (IMARs).
- Permanently discontinue for life-threatening (Grade 4) IMARs, recurrent severe (Grade 3) IMARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Drug Availability

- 240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL) single-dose 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), dermatologic adverse reactions, nephritis with renal dysfunction, and myocarditis.
- 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 fatal and other serious complications including hyperacute graft-versus-host-disease (GVHD), acute or chronic GVHD, steroid-requiring febrile syndrome, and hepatic veno-occlusive disease.
- Embryofetal toxicity: can cause fetal harm. Advise of potential risk to fetus and use of effective contraception.

BILLING/CODING INFORMATION:

HCPCS Coding

J9298	Injection, nivolumab and relatlimab-rmbw, 3 mg/1 mg

ICD-10 Diagnosis Codes That Support Medical Necessity

C43.0 – C43.9	Malignant melanoma of skin

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 review date.

DEFINITIONS:

None

RELATED GUIDELINES:

None

OTHER:

Table 1: 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

REFERENCES:

1. Clinical Pharmacology [Internet]. Tampa (FL): Gold Standard, Inc.; 2024 [cited 2024 Apr 24]. Available from: http://www.clinicalpharmacology.com/.
2. DRUGDEX® System [Internet]. Greenwood Village (CO): Thomson Micromedex; Updated periodically [cited 2024 Apr 24].
3. National Cancer Institute. Common Terminology Criteria for Adverse Events. Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm. Accessed 04/24/24.
4. National Comprehensive Cancer Network®. NCCN clinical practice guidelines in oncology (NCCN Guidelines®). Cutaneous melanoma, v2.2024.. Available from: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed 04/24/24.
5. NCCN Drugs & Biologics Compendium [Internet]. Fort Washington (PA): National Comprehensive Cancer Network;2024. Available from: http://www.nccn.org/professionals/drug_compendium/content/contents.asp/. Accessed 04/24/24.
6. Opdualag (nivolumab;relatlimab-rmbw) injection [package insert]. Bristol-Myers Squibb Company. Princeton, NJ. March 2024.
7. Orphan Drug Designations and Approval [Internet]. Silver Spring (MD): US Food and Drug Administration; 2024 [cited 2024 Apr 24]. Available from: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm/.

COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/08/24.

GUIDELINE UPDATE INFORMATION:

06/15/22	New Medical Coverage Guideline.
10/01/22	Revision: Added HCPCS code J9298 and deleted code J9999.
05/15/23	Review and revision to guideline; consisting of updating position statement to include second line or subsequent therapy.
06/15/24	Review and revision to guideline; consisting of updating position statement to include neoadjuvant treatment.