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Subject: Apalutamide (Erleada®) Tablet

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:

Apalutamide (Erleada) is an oral androgen receptor (AR) inhibitor initially approved by the U.S. Food and Drug Administration (FDA) in February 2018 for the treatment of patients with non-metastatic, castration-resistant prostate cancer (CRPC). Apalutamide binds directly to the ligand-binding domain of the AR which inhibits AR nuclear translocation, inhibits DNA binding, and impedes AR-mediated transcription. This ultimately results in decreased tumor cell proliferation and increased apoptosis leading to decreased tumor volume. Apalutamide is the first drug approved by the FDA for the treatment of patients with non-metastatic CRPC (NM-CRPC). Treatment of NM-CRPC has been considered an area of unmet need, as patients had to develop distant metastases before being candidates for the various FDA-approved drugs for the treatment of metastatic CRPC.

Prostate cancer remains the most common non-cutaneous malignancy among men worldwide. Prostate cancer is a complex disease with many variable aspects of management. Prostate cancer is an androgen dependent disease that initially responds but later becomes resistant to established therapies that reduce circulating testosterone levels or inhibit androgen binding to the AR. Reactivation of the disease despite castrate levels of testosterone represents a transition to the lethal phenotype of CRPC. This state is now recognized to be driven by AR signaling, in part due to overexpression of the androgen receptor itself. While various options are FDA approved for the treatment of metastatic CRPC, the treatment of NM-CRPC has been a therapeutic challenge. Prior to apalutamide no drug had been approved in this patient population to help reduce the risk of progression to metastatic disease.

The safety and efficacy of apalutamide leading to FDA approval was established in a multicenter, double-blind, randomized, placebo-controlled clinical trial called SPARTAN. A total of 1,207 patients with NM-CRPC were randomized (2:1) to receive either apalutamide 240 mg once daily (n=806) or placebo

(n=401). All patients received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients were required to have a PSADT (prostate specific antigen doubling time) of ≤10 months and confirmation of non-metastatic disease by blinded independent central review (BICR). The PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression, locoregional-only progression, initiation of new treatment, unacceptable toxicity, or withdrawal. The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 74 years (range 48 to 97) and 26% of patients were 80 years of age or older. The racial distribution was 66% Caucasian, 12% Asian, and 6% Black. Seventy-seven percent (77%) of patients in both treatment arms had prior surgery or radiotherapy of the prostate. A majority of patients had a Gleason score of 7 or higher (78%). Fifteen percent (15%) of patients had <2 cm pelvic lymph nodes at study entry. Seventy-three percent (73%) of patients received prior treatment with an anti-androgen; 69% of patients received bicalutamide and 10% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. Among the patients who discontinued study treatment (n=279 for placebo and n=314 for apalutamide), a greater proportion (80%) of patients treated with placebo received subsequent therapy compared to patients treated with apalutamide (56%). Locoregional-only progression occurred in 2% of patients overall. The median duration of exposure was 16.9 months (range: 0.1 to 42 months) in patients who received apalutamide and 11.2 months (range: 0.1 to 37 months) in patients who received placebo.

The primary efficacy outcome measure was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of BICR-confirmed distant metastasis, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first. Additional efficacy endpoints were time to metastasis (TTM), progression-free survival (PFS) which also includes locoregional progression, time to symptomatic progression, and overall survival (OS). A statistically significant improvement in MFS of 24.3 months was demonstrated in patients randomized to receive apalutamide vs. placebo. Consistent results were observed across patient subgroups including PSADT (≤6 months or >6 months), use of a prior bone-sparing agent (yes or no), and locoregional disease (N0 or N1). The major efficacy outcome was supported by statistically significant improvements in TTM, PFS, and time to symptomatic progression. Overall survival (OS) data were not mature at the time of final MFS analysis (24% of the required number of events). The efficacy results of MFS, TTM, and PFS are summarized in Table 1 below.

Table 1: BICR-Assessed Efficacy Results from the SPARTAN Trial

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value
	Erleada (N=806)	Placebo (N=401)	Erleada	Placebo	
Metastasis Free Survival	184 (23%)	194 (48%)	40.5 (NE, NE)	16.2 (14.6, 18.4)	0.28 (0.23, 0.35) <0.0001
Time to Metastasis	175 (22%)	191 (48%)	40.5 (NE, NE)	16.6 (14.6, 18.5)	0.27 (0.22, 0.34) <0.0001

Endpoint	Number of Events (%)		Median [Months (95% CI)]		HR (95% CI) p-value
	Erleada (N=806)	Placebo (N=401)	Erleada	Placebo	
Progression-Free Survival	200 (25%)	204 (51%)	40.5 (NE, NE)	14.7 (14.5, 18.4)	0.29 (0.24, 0.36) <0.0001
NE = not estimable					

The rate of adverse events leading to discontinuation of the trial regimen was 10.6% in the apalutamide group and 7% in the placebo group. The following adverse events occurred at a higher rate with apalutamide than with placebo: rash (23.8% vs. 5.5%), hypothyroidism (8.1% vs. 2.0%), and fracture (11.7% vs. 6.5%).

The National Comprehensive Cancer Network (NCCN) Prostate Cancer Guidelines (Version 2.2018) list apalutamide as a category 1 treatment option for non-metastatic (M0), castration-resistant prostate cancer (CRPC). The NCCN defines CRPC as prostate cancer that progresses clinically, radiologically, or biochemically despite castrate levels of serum testosterone (<50 ng/dL). If disease progression is observed during ADT, imaging studies (e.g., chest X-ray or CT, bone imaging, and abdominal CT or MRI) should be conducted to rule out distant metastases. If distant metastases are absent (i.e., M0), the NCCN recommends the continuation of ADT to maintain castrate serum levels and then three different management options: (1) observation especially if PSADT >10 months [category 2A], (2) apalutamide especially if PSADT ≤10 months [category 1], and (3) other secondary hormone therapy especially if PSADT ≤10 months [category 2A]. The applicable secondary hormone therapies include flutamide, bicalutamide, nilutamide, ketoconazole ± hydrocortisone, a corticosteroid, diethylstilbestrol (DES), or other estrogen. If PSA levels are not increasing, the current treatment should be maintained with continued monitoring. If PSA is increasing but there are no distant metastases, then treatment can be either changed or maintained with continued monitoring. If metastases develop, the various treatment options for metastatic (M1) CRPC should then be considered.

POSITION STATEMENT:

Comparative Effectiveness

The FDA has deemed the drug(s) or biological product(s) in this coverage policy to be appropriate for self-administration or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage (i.e., administration) in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility is not considered medically necessary.

Initiation of apalutamide (Erleada) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1" to "4"):

1. Member has a diagnosis of non-metastatic (M0), castration-resistant prostate cancer (NM-CRPC) as defined by **BOTH** of the following ("a" and "b"):

a. Member is receiving continuous androgen deprivation therapy (ADT) and has disease that has progressed clinically, radiologically, or biochemically - lab documentation of a recent (past 90 days) serum testosterone level at castrate level (<50 ng/dL) must be submitted for members receiving medical castration. A chart note documenting a bilateral orchiectomy must be submitted for members who have received surgical castration.

b. There is no evidence of distant metastases as assessed by appropriate imaging studies (e.g., chest X-ray or chest CT, bone imaging, and abdominal/pelvic CT or MRI with and without contrast) taken after disease progression on ADT but before initiation of apalutamide therapy

2. Member will continue to receive ADT during treatment with apalutamide
3. Dosage of apalutamide does not exceed 240 mg (four 60 mg tablets) once daily
4. Apalutamide is not used concomitantly with **ANY** of the following:
   a. abiraterone (Zytiga)
   b. cabazitaxel (Jevtana)
   c. docetaxel (Taxotere)
   d. first generation anti-androgen (i.e., bicalutamide, flutamide, or nilutamide
   e. mitoxantrone (Novantrone)
   f. radium-223 (Xofigo)
   g. sipuleucel-T (Provenge)

Approval duration: 6 months

Continuation of apalutamide (Erleada) **meets the definition of medical necessity** when **ALL** of the following criteria are met ("1 to "5"):

1. An authorization or reauthorization for apalutamide has been previously approved by Florida Blue or another health plan in the past 2 years for the treatment of non-metastatic, castration-resistant prostate cancer, **OR** the member has previously met **ALL** indication-specific criteria
2. Member will continue to receive ADT (i.e., either medically-induced or surgical-induced castration) during treatment with apalutamide
3. Member has not developed distant metastases during treatment with apalutamide – members with evidence of clinical or biochemical disease progression should be assessed for metastases by appropriate imaging studies
4. Dosage of apalutamide does not exceed 240 mg (four 60 mg tablets) once daily
5. Apalutamide is not taken concomitantly with **ANY** of the following:
   a. abiraterone (Zytiga)
   b. cabazitaxel (Jevtana)
   c. docetaxel (Taxotere)
   d. first generation anti-androgens (i.e., bicalutamide, flutamide, or nilutamide)

e. mitoxantrone (Novantrone)

f. radium-223 (Xofigo)

g. sipuleucel-T (Provenge)

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

- For the treatment of patients with non-metastatic, castration-resistant prostate cancer (NM-CRPC)
- The recommended dose is 240 mg (four 60 mg tablets) administered orally once daily. Swallow the tablets whole with or without food. Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Dose Adjustments

- **Hepatic impairment**: Specific guidelines for dosage adjustments in hepatic impairment are not available; it appears that no dosage adjustments are needed.
- **Renal impairment**: Specific guidelines for dosage adjustments in renal impairment are not available; it appears that no dosage adjustments are needed.
- **Grade 3 or higher toxicity or intolerable adverse reaction**: Hold apalutamide. When symptoms improve to grade 1 or less (or original grade), resume apalutamide therapy at the same dose or a reduced dose (180 mg or 120 mg), if warranted.

Drug Availability

- 60 mg film-coated tablets in bottles of 120 tablets
- Store in the original package. Do not discard desiccant. Protect from light and moisture.

PRECAUTIONS:

Boxed Warning

- None

Contraindications

- **Pregnancy**: can cause fetal harm and potential loss of pregnancy. Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of apalutamide.

Precautions/Warnings

- **Falls and Fractures**: Falls and fractures occurred in patients receiving apalutamide. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone targeted agents. In the phase III trial leading to FDA approval, falls occurred in 16% of patients treated with apalutamide vs. 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 12% of patients treated with apalutamide vs. 7% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with apalutamide.
- **Seizure:** Seizure occurred in two (0.2%) of patients receiving apalutamide. Permanently discontinue in patients who develop a seizure during treatment. There is no clinical experience in re-administering apalutamide to patients who experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with apalutamide. Advise patients of the risk of developing a seizure while receiving apalutamide and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.
- **Drug Interactions:**
    - **Strong CYP2C8 or CYP3A4 Inhibitors**: Co-administration of a strong CYP2C8 inhibitor (e.g., gemfibrozil) or CYP3A4 inhibitor (e.g., ketoconazole) is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however; reduce the apalutamide dose based on tolerability. Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.
    - **CYP3A4, CYP2C9, CYP2C19 and UGT Substrates**: Apalutamide is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of apalutamide with medications that are primarily metabolized by CYP3A4 (e.g., midazolam), CYP2C19 (e.g., omeprazole), or CYP2C9 (e.g., warfarin) can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of apalutamide with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with apalutamide and evaluate for loss of activity.
    - **P-gp, BCRP or OATP1B1 Substrates**: Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) by 30% and rosuvastatin (a BCRP/OATP1B1 substrate) by 41%. Concomitant use of apalutamide with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with apalutamide and evaluate for loss of activity if medication is continued.

BILLING/CODING INFORMATION:

The following codes may be used to describe:

HCPCS Coding

C9399	Unclassified drugs or biologicals (Hospital Outpatient Use ONLY)

J8999	Prescription drug, oral, chemotherapeutic, not otherwise specified

ICD-10 Diagnosis Codes That Support Medical Necessity

C61	Malignant neoplasm of prostate

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: BCBSF 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 guideline creation.

DEFINITIONS:

Castrate-resistant/recurrent prostate cancer (CRPC): disease progression despite androgen deprivation therapy (ADT) with either medication or surgery (i.e., removal/destruction of testicles), and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases.

TNM Classification of Malignant Tumors (TNM): a notation system that describes the stage of a cancer which originates from a solid tumor with alphanumeric codes. T describes the size of the original (primary) tumor and whether it has invaded nearby tissue. N describes nearby (regional) lymph nodes that are involved, M describes distant metastasis (spread of cancer from one part of the body to another).

RELATED GUIDELINES:

Abiraterone acetate (Zytiga), 09-J1000-36

Cryosurgical Ablation of the Prostate (CSAP), 02-54000-14

Docetaxel (Taxotere) IV, 09-J0000-95

Enzalutamide (Xtandi) Capsules, 09-J1000-85

Gonadotropin Releasing Hormone Analogs and Antagonists, 09-J0000-48

OTHER:

None

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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Pharmacy Policy Committee on 05/09/18.

GUIDELINE UPDATE INFORMATION:

06/15/18	New Medical Coverage Guideline.