PHARMACY COVERAGE GUIDELINE

NUBEQA™ (darolutamide) oral
XTANDI® (enzalutamide) oral

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require precertification is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

➢ **Criteria for initial therapy:** Xtandi (enzalutamide) or Nubeqa (darolutamide) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Urologist.

2. Individual is 18 years of age or older.

3. Individual has a confirmed diagnosis of **ONE** of the following:
    a. **For Nubeqa (darolutamide) only:**
        i. Non-metastatic (M0) castration-resistant prostate cancer (nmCRPC)

b. **For Xtandi (enzalutamide) only:**
   i. Prostate cancer is **ONE** of the following:
      1. Castration resistant prostate cancer (CRPC)
      2. Metastatic castration sensitive prostate (mCSPC)

c. Other request for a specific oncologic direct treatment use that is found and listed in the National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

4. Individual will use requested agent in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (< 50 ng/dL) unless has had bilateral orchiectomy.

5. **ONE** of the following:
   a. **For Nubeqa: BOTH** of the following
      i. Individual is not on hemodialysis or end stage renal disease (eGFR less than or equal to 15 mL/min/1.73m^2)
      ii. Individual does not have severe hepatic impairment (Child-Pugh Class C)
   b. **For Xtandi:**
      i. Individual does not have severe renal impairment (CrCl less than 30 mL/min) or end-stage renal disease

6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

7. **For Nubeqa** individual is not using drugs that are combined P-gp and strong or moderate CYP3A inducers (ex., carbamazepine, phenobarbital, phenytoin, rifampin, dexamethasone, Saint John's wort, etc.).

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Xtandi (enzalutamide) or Nubeqa (darolutamide) is considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy**):

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Oncologist or Urologist.

2. Individual's condition has responded while on therapy with response defined as **ALL** of the following:
   a. No evidence of disease progression
   b. Documented evidence of efficacy, disease stability and/or improvement

3. Individual has been adherent with the medication.

4. **ONE** of the following:
   a. **For Nubeqa: ALL** of the following
      i. Requested dose is at least 300 mg twice daily
      ii. Individual is not on hemodialysis

iii. Individual does not have severe hepatic impairment (Child-Pugh Class C)

b. **For Xtandi:**
   i. Individual does not have severe renal impairment (CrCl less than 30 mL/min) or end-stage renal disease

5. Individual is using requested agent in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (< 50 ng/dL) unless has had bilateral orchiectomy.

6. Individual has not developed any significant adverse drug effects that may exclude continued use such as:
   a. Posterior reversible encephalopathy syndrome (PRES) with Xtandi
   b. Seizure while on Xtandi
   c. Edema of face, tongue, or lip or any symptoms of hypersensitivity
   d. Severe ischemic heart disease

7. **For Nubeqa** individual is not using drugs that are combined P-gp and strong or moderate CYP3A inducers (ex., carbamazepine, phenobarbital, phenytoin, rifampin, dexamethasone, Saint John's wort, etc.)

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

Description:

Xtandi (enzalutamide) is an androgen receptor inhibitor indicated for **the treatment of castration-resistant prostate cancer (CRPC) and metastatic castration-sensitive prostate cancer (mCSPC)**. Nubeqa (darolutamide) is an androgen receptor inhibitor indicated for **the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).** Patients receiving either Xtandi (enzalutamide) or Nubeqa (darolutamide) should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Enzalutamide and darolutamide act on different steps in the androgen receptor signaling pathway. They have been shown to competitively inhibit androgen binding to androgen receptors and inhibit androgen receptor nuclear translocation and interaction with deoxyribonucleic acid (DNA). Enzalutamide and darolutamide decrease proliferation and induce cell death of prostate cancer cells *in vitro*, and decrease tumor volume in a mouse prostate cancer xenograft model.

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Definitions:

Antiandrogens, oral:
- Zytiga (abiraterone acetate)
- Erleada (apalutamide)
- Bicalutamide
- Nubeqa (darolutamide)
- Xtandi (enzalutamide)
- Flutamide
- Nilutamide

Gonadotropin-releasing hormone (GnRH) agonists: also referred to as luteinizing hormone releasing hormone (LHRH) agonists or analogues:
- Zoladex (goserelin acetate) subcutaneous implant
- Vantas (histrelin acetate) subcutaneous implant
- Eligard (leuprolide acetate) subcutaneous injection
- Lupron Depot (leuprolide acetate) intramuscular injection
- Trelstar (triptorelin pamoate) intramuscular injection

Gonadotropin-releasing hormone antagonist:
- Firmagon (dagarelix) subcutaneous injection

Resources:

Nubeqa (darolutamide) product information, revised by Bayer HealthCare Pharmaceuticals, Inc. 01-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 04, 2022.

Xtandi (enzalutamide) capsule and tablet product information, revised by Astellas Pharma US, Inc. 01-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed August 04, 2022.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer Version 4.2022 – Updated May 10, 2022. Available at https://www.nccn.org. Accessed August 04, 2022.

Off Label Use of Cancer Medications: A.R.S. §§ 20-826(R) & (S). Subscription contracts; definitions.

Off Label Use of Cancer Medications: A.R.S. §§ 20-1057(V) & (W). Evidence of coverage by health care service organizations; renewability; definitions.