PHARMACY COVERAGE GUIDELINES	**ORIGINAL EFFECTIVE DATE: 1/01/2016**
SECTION: DRUGS	**LAST REVIEW DATE: 8/19/2021**
	LAST CRITERIA REVISION DATE: 8/19/2021
	ARCHIVE DATE:

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

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Pharmacy Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.

This Pharmacy Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide BCBSAZ complete medical rationale when requesting any exceptions to these guidelines.

The section identified as "Description" defines or describes a service, procedure, medical device or drug and is in no way intended as a statement of medical necessity and/or coverage.

The section identified as "Criteria" defines criteria to determine whether a service, procedure, medical device or drug is considered medically necessary or experimental or investigational.

State or federal mandates, e.g., FEP program, may dictate that any drug, device or biological product approved by the U.S. Food and Drug Administration (FDA) may not be considered experimental or investigational and thus the drug, device or biological product may be assessed only on the basis of medical necessity.

Pharmacy Coverage Guidelines are subject to change as new information becomes available.

For purposes of this Pharmacy Coverage Guideline, the terms "experimental" and "investigational" are considered to be interchangeable.

This Pharmacy Coverage Guideline does not apply to FEP or other states' Blues Plans.

Information about medications that require precertification is available at www.azblue.com/pharmacy.

Some large (100+) benefit plan groups may customize certain benefits, including adding or deleting precertification requirements.

All applicable benefit plan provisions apply, e.g., waiting periods, limitations, exclusions, waivers and benefit maximums.

Precertification for medication(s) or product(s) indicated in this guideline requires completion of the request form in its entirety with the chart notes as documentation. **All requested data must be provided.** Once completed the form must be signed by the prescribing provider and faxed back to BCBSAZ Pharmacy Management at (602) 864-3126 or emailed to Pharmacyprecert@azblue.com. **Incomplete forms or forms without the chart notes will be returned.**

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Criteria:

- **Criteria for initial therapy:** Xtandi (enzalutamide) or Nubeqa (darolutamide) is considered ***medically necessary*** and will be approved when **ALL** of 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 male and 18 years of age or older

  3. A confirmed diagnosis of **ONE** of the following:

     a. **For Nubeqa (darolutamide) only:**
        i. Non-metastatic (M0) castration-resistant prostate cancer (nmCRPC) with a PSA doubling time (PSADT) ≤ 10 months

     b. **For Xtandi (enzalutamide) only:**
        i. Prostate cancer 1s **ONE** of the following:
           1. Metastatic castration resistant prostate cancer (mCRPC) in either patient who received chemotherapy or in chemotherapy-naïve patients

           2. Non-metastatic (M0) castration-resistant prostate cancer (nmCRPC) with a PSA doubling time (PSADT) ≤ 10 months and PSA ≥ 2 ng/mL

           3. 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
        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. There are no significant interacting drugs

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 with documentation of **ALL** of the following:

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 responded while on therapy
    a. Response is defined as:
        i. No evidence of disease progression
        ii. 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
    a. Significant adverse effects such as:
        i. Posterior reversible encephalopathy syndrome (PRES) with Xtandi
        ii. Seizure while on Xtandi
        iii. Edema of face, tongue, or lip or any symptoms of hypersensitivity
        iv. Severe ischemic heart disease

7. There are no significant interacting drugs

Renewal duration: 12 months

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- 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 a Non-cancer Medications**

  2. **Off-Label Use of a Cancer Medication for the Treatment of Cancer without a Specific Coverage Guideline**

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.

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 (leuroplide acetate) subcutaneous injection
Lupron Depot (leuprolide acetate) intramuscular injection
Trelstar (triptorelin pamoate) intramuscular injection

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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 on July 28, 2021.

Xtandi (enzalutamide) product information, revised by Astellas Pharma US, Inc. 07-2021. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed on July 28, 2021.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer Version 2.2021 – Updated February 17, 2021. Available at https://www.nccn.org. Accessed on July 28, 2021.

Klein EA. Prostate cancer: Risk stratification and choice of initial treatment. In: UpToDate, Volgelzang N, Lee WR, Richie JP, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on July 29, 2021.

Dawson NA, Leger P. Overview of the treatment of castration-resistant prostate cancer (CRPC). In: UpToDate, Volgelzang N, Lee WR, Richie JP, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on July 29, 2021.

Dawson NA. Overview of systemic treatment for advanced, recurrent and metastatic castration-sensitive prostate cancer and local treatment for men with metastatic disease. In: UpToDate, Volgelzang N, Lee WR, Richie JP, Savarese DMF (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Accessed on July 29, 2021.

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.