BlueCross BlueShield Arizona

An Independent Licensee of the Blue Cross Blue Shield Association

PHARMACY COVERAGE GUIDELINE

NUBEQA™ (darolutamide) oral
XTANDI® (enzalutamide) oral
Generic Equivalent (if available)

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 prior authorization 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), Nubeqa (darolutamide), and/or generic equivalent (if available) 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. Prostate cancer is **ONE** of the following:

1. Non-metastatic (M0) castration-resistant prostate cancer (nmCRPC)
2. Metastatic hormone sensitive prostate cancer (mHSPC) in combination with docetaxel

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)
      3. Non-metastatic (M0) castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR)

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 (less than 50 ng/dL) unless has had bilateral orchiectomy (**Does not apply for Xtandi for nmCSPC with high-risk BCR**)

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. **ONE** of the following:
   a. **For Nubeqa: ALL** of the following
      i. Individual is not on hemodialysis and does not have 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)
      iii. Individual will use requested agent in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL) unless has had bilateral orchiectomy
   b. **For Xtandi:**
      i. Individual does not have severe renal impairment (CrCl less than 30 mL/min) or end-stage renal disease

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

8. **For Nubeqa only:** Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with combined P-gp and strong or moderate CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, dexamethasone, Saint John's wort, etc.)

Initial approval duration: 6 months

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- **Criteria for continuation of coverage (renewal request):** Xtandi (enzalutamide), Nubeqa (darolutamide), and/or generic equivalent (if available) 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 there is no evidence of disease progression or unacceptable toxicity

  3. Individual has been adherent with the medication

  4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

  5. **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

  6. Individual will use requested agent in combination with a gonadotropin-releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL) unless has had bilateral orchiectomy (**Does not apply for Xtandi for nmCSPC with high-risk BCR**)

  7. 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. Edema of face, tongue, or lip, pharyngeal edema, or any symptoms of hypersensitivity with Xtandi
     c. Seizure
     d. Severe ischemic heart disease

  8. **For Nubeqa:** Individual is not currently taking any other drugs which cause severe adverse reactions or any drug interactions requiring discontinuation such as use with combined P-gp and strong or moderate CYP3A inducers (e.g., 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:

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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), metastatic castration-sensitive prostate cancer (mCSPC) and non-metastatic (M0) castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis**. Nubeqa (darolutamide) is an androgen receptor inhibitor indicated for **the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC) and for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel in adults.** 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. Patients with nmCSPC with high-risk BCR may be treated with Xtandi with or without a GnRH analog.

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:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

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

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

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status	
Grade	ECOG 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 housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, 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
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982	

NCCN recommendation definitions:
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 is 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

Resources:

Nubeqa (darolutamide) product information, revised by Bayer HealthCare Pharmaceuticals, Inc. 10-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 15, 2024.

Xtandi (enzalutamide) capsule and tablet product information, revised by Astellas Pharma US, Inc. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed July 15, 2024.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer Version 4.2024. Updated May 17, 2024. Available at https://www.nccn.org. Accessed July 15, 2024.

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.