

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/or 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.
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Medical Necessity Requirements for NUBEQA (darolutamide)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an Oncologist or Urologist or in consultation with an Oncologist or Urologist

Indication

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

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- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Will use in combination with a gonadotropin releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL), unless bilateral orchiectomy has been performed
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (FDA)

Safety

- **NONE** of the following:
 - Hemodialysis or end stage renal disease (eGFR less than or equal to 15 mL/min/1.73m²)
 - Severe hepatic impairment (Child Pugh Class C)
 - Concomitant use with P glycoprotein and strong or moderate CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, dexamethasone, Saint John's wort, etc.)

Documentation Requirements

- A completed request form must be submitted, including:
 - Chart notes
 - Lab results
 - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or is in consultation with an Oncologist or Urologist

Clinical Response

- No evidence of disease progression or unacceptable toxicity

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- Used in combination with a gonadotropin releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL), unless bilateral orchiectomy has been performed

Adherence

- Adherence to the prescribed therapy regimen has been documented
- Requested dose is at least 300 mg twice daily

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- **NONE** of the following:
 - Hemodialysis or end stage renal disease (eGFR less than or equal to 15 mL/min/1.73m²)
 - Severe hepatic impairment (Child Pugh Class C)
 - Concomitant use with P glycoprotein and strong or moderate CYP3A inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifampin, dexamethasone, Saint John's wort, etc.)
 - Significant adverse drug effects that may exclude continued use such as:
 1. Seizure
 2. Severe ischemic heart disease

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year
-

Medical Necessity Requirements for XTANDI (enzalutamide)

Criteria for Initial Therapy:

Prescriber Qualifications

- Prescribed by an Oncologist or Urologist or in consultation with an Oncologist or Urologist

Indication

- Castration resistant prostate cancer (CRPC)

ORIGINAL EFFECTIVE DATE: 01/01/2016 | ARCHIVE DATE: | LAST REVIEW DATE: 08/21/2025 | LAST CRITERIA REVISION DATE: 08/21/2025

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

- Metastatic castration sensitive prostate cancer (mCSPC)
- Non metastatic (M0) castration sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis
- Other oncologic direct treatment use listed in National Comprehensive Cancer Network (NCCN) Guidelines with Categories of Evidence and Consensus of 1 and 2A

Age Requirement

- 18 years or older

Baseline Clinical Evaluation

- Will use in combination with a gonadotropin releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL), unless bilateral orchiectomy has been performed [Note: For nmCSPC with high risk biochemical recurrence, may be treated with Xtandi with or without a GnRH analog]
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the U.S. Food and Drug Administration (FDA)

Safety

- Does not have severe renal impairment (CrCl less than 30 mL/min) or end stage renal disease

Documentation Requirements

- A completed request form must be submitted, including:
 - Chart notes
 - Lab results
 - Supporting clinical documentation

Initial Therapy Criteria Approval Duration:

- 6 months OR end of plan year
-

Criteria for Continuation of Therapy (renewal therapy)

Note: Manufacturer assistance (e.g., coupons, samples, etc.) are not considered for continuation of therapy

Prescriber Qualification

- Continues to be seen by a physician specializing in or is in consultation with an Oncologist or Urologist

Clinical Response

- No evidence of disease progression or unacceptable toxicity

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- Used in combination with a gonadotropin releasing hormone (GnRH) agonist or antagonist to maintain castrate serum testosterone levels (less than 50 ng/dL), unless bilateral orchiectomy has been performed [Note: For nmCSPC with high risk biochemical recurrence, may be treated with Xtandi with or without a GnRH analog]

Adherence

- Adherence to the prescribed therapy regimen has been documented

Brand Specific Criteria

- Have failure, contraindication, or intolerance with **THREE** generic equivalents (when available) for at least three months each. **Note:** Any failure, contraindication, or intolerance to the generic drugs should be reported to the FDA (see Definitions section)

Safety

- Does not have severe renal impairment (CrCl less than 30 mL/min) or end stage renal disease
- Has not developed any significant adverse drug effects that may exclude continued use such as:
 - Posterior reversible encephalopathy syndrome
 - Edema of face, tongue, or lip, pharyngeal edema, or hypersensitivity symptoms
 - Seizure
 - Severe ischemic heart disease

Documentation Requirements

- Chart notes
- Supporting clinical documentation with evidence of improvement in given indication
- Lab values that confirm safe use

Continuation Therapy Criteria Approval Duration:

- 12 months OR end of plan year
-

Criteria for Off-Label Use Requests:

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

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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

Gonadotropin-releasing hormone antagonist:

Firmagon (dagarelix) subcutaneous injection

ECOG Performance status:

Eastern Co-operative Oncology Group (ECOG) Performance Status

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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 May 09, 2025.

Xtandi (enzalutamide) capsule and tablet product information, revised by Astellas Pharma US, Inc. 03-2025. Available at DailyMed <http://dailymed.nlm.nih.gov>. Accessed May 09, 2025.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer Version 2.2025. Updated April 16, 2025. Available at <https://www.nccn.org>. Accessed May 09, 2025.

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.