# Clinical Policy: Enzalutamide (Xtandi)

Reference Number: CP.PHAR.106
Effective Date: 10.12
Last Review Date: 02.23
Line of Business: Commercial, HIM, Medicaid

Revision Log

**See Important Reminder at the end of this policy for important regulatory and legal information.**

## Description

Enzalutamide (Xtandi®) is an androgen receptor inhibitor.

## FDA Approved Indication(s)

Xtandi is indicated for the treatment of patients with:

- Castration-resistant prostate cancer (CRPC)
- Metastatic castration-sensitive prostate cancer (CSPC)

## Policy/Criteria

*Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.*

It is the policy of health plans affiliated with Centene Corporation® that Xtandi is **medically necessary** when the following criteria are met:

**I. Initial Approval Criteria**

**A. Prostate Cancer** (must meet all)**:**

1. Diagnosis of one of the following (a or b):
   a. CRPC, as evidenced by disease progression despite bilateral orchiectomy or other androgen deprivation therapy (ADT) (*see Appendix D*);
   b. Metastatic CSPC;
2. Prescribed by or in consultation with an oncologist or urologist;
3. Age ≥ 18 years;
4. For Xtandi requests, member must use generic enzalutamide, if available, unless contraindicated or clinically significant adverse effects are experienced;
5. Prescribed concurrently with a gonadotropin-releasing hormone (GnRH) analog or member has had a bilateral orchiectomy;
6. Request meets one of the following (a, b, c, or d):*
   a. If prescribed concomitantly with a strong CYP2C8 inhibitor (e.g., gemfibrozil): Dose does not exceed 80 mg (2 capsules or 1 tablet) per day;
   b. Dose does not exceed 160 mg (4 capsules or 2 tablets) per day;
   c. If prescribed concomitantly with a strong CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital): Dose does not exceed 240 mg (6 capsules or 3 tablets) per day;
   d. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

**Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 6 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

**II. Continued Therapy**

**A. Prostate Cancer** (must meet all)**:**
1. Currently receiving medication via Centene benefit, or documentation supports that member is currently receiving Xtandi for prostate cancer and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. For Xtandi requests, member must use generic enzalutamide, if available, unless contraindicated or clinically significant adverse effects are experienced;
4. If request is for a dose increase, request meets one of the following (a, b, c, or d):*
   a. If prescribed concomitantly with a strong CYP2C8 inhibitor (e.g., gemfibrozil): New dose does not exceed 80 mg (2 capsules or 1 tablet) per day;
   b. New dose does not exceed 160 mg (4 capsules or 2 tablets) per day;
   c. If prescribed concomitantly with a strong CYP3A4 inducer (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, and phenobarbital): New dose does not exceed 240 mg (6 capsules or 3 tablets) per day;
   d. New dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (*prescriber must submit supporting evidence*).

   **Prescribed regimen must be FDA-approved or recommended by NCCN*

**Approval duration: 12 months**

**B. Other diagnoses/indications** (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

## III. Diagnoses/Indications for which coverage is NOT authorized:

**A.** Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid or evidence of coverage documents.

## IV. Appendices/General Information

*Appendix A: Abbreviation/Acronym Key*

ADT: androgen deprivation therapy
CRPC: castration-resistant prostate cancer
CSPC: castration-sensitive prostate cancer
FDA: Food and Drug Administration
GnRH: gonadotropin-releasing hormone
LHRH: luteinizing hormone-releasing hormone
NCCN: National Comprehensive Cancer Network

*Appendix B: Therapeutic Alternatives*

| Drug Name | Dosing Regimen | Dose Limit/ Maximum Dose |
|---|---|---|
| abiraterone (Zytiga®) | 1,000 mg (four 250 mg tablets) PO QD in combination with prednisone 5 mg PO BID (CRPC) or prednisone 5 mg PO QD (CSPC) | 1,000 mg QD; 1,000 mg BID if taking a strong CYP3A4 inducer |

*Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.*

*Appendix C: Contraindications/Boxed Warnings*

None reported

*Appendix D: General Information*

- CRPC is prostate cancer that progresses clinically, radiographically, or biochemically despite castrate levels of serum testosterone (< 50 ng/dL). Per the NCCN, ADT should be continued in the setting of CRPC while additional therapies are applied.
  - Examples of ADT include:
    - Bilateral orchiectomy (surgical castration)
    - Luteinizing hormone-releasing hormone (LHRH) agonist given with or without an anti-androgen:

- LHRH agonists: Zoladex® (goserelin), Vantas® (histrelin), leuprolide (Lupron Depot®, Eligard®), and Trelstar® (triptorelin)
- Anti-androgens: bicalutamide (Casodex®), flutamide (Eulexin®), nilutamide (Nilandron®), Xtandi® (enzalutamide), Erleada® (apalutamide)

▪ LHRH antagonist: Firmagon® (degarelix), Orgovyx® (relugolix)

## V. Dosage and Administration

| Indication | Dosing Regimen | Maximum Dose |
|---|---|---|
| CRPC, metastatic CSPC | 160 mg (two 80 mg tablets) PO QD. Patients receiving Xtandi should also receive a GnRH analog concurrently or should have had bilateral orchiectomy | 160 mg/day; 240 mg/day if taking a strong CYP3A4 inducer |

## VI. Product Availability

- Capsule: 40 mg
- Tablets: 40 mg, 80 mg

## VII. References

1. Xtandi Prescribing Information. Northbrook, IL: Astellas Pharma US.; September 2022. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203415s019,213674s006lbl.pdf. Accessed September 19, 2022.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed September 19, 2022.
3. National Comprehensive Cancer Network. Prostate Cancer Version 1.2023. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed September 19, 2022.
4. Virgo KS, Basch E, Loblaw DA, et al. Second-Line Hormonal Therapy for Men with Chemotherapy-Naïve Castration-Resistant Prostate Cancer. American Society of Clinical Oncology (ASCO). Published online April 25, 2017, DOI: 10.1200/JCO.2017.72.8030. Available at: https://www.asco.org/practice-patients/guidelines/genitourinary-cancer#/25251. Accessed January 19, 2022.
5. Virgo KS, Rumble B, de Wit R, et al. Initial Management of Non-Castrate Advanced, Recurrent or Metastatic Prostate Cancer. American Society of Clinical Oncology (ASCO). Published ahead of print January 26, 2021, DOI: 10.1200/JCO.20.03256. Available at: https://www.asco.org/practice-patients/guidelines/genitourinary-cancer#/9521. Accessed January 19, 2022.
6. Basch E, Loblaw DA, Oliver TK, et al. Systemic Therapy in Men with Metastatic Castration-Resistant Prostate Cancer (CRPC). American Society of Clinical Oncology (ASCO). Published online before print September 8, 2014. Available at: https://www.asco.org/practice-patients/guidelines/genitourinary-cancer#/9496. Accessed January 19, 2022.

| Reviews, Revisions, and Approvals | Date | P&T Approval Date |
|---|---|---|
| Criteria added for new FDA indication: non-metastatic CRPC; removed requirement for metastatic disease as Xtandi is now approved for non-metastatic prostate cancer; added requirement for non-metastatic disease that Xtandi be used with a GnRH analog or member has had a bilateral orchiectomy; added urologist prescriber option; references reviewed and updated. | 08.28.18 | 02.19 |
| 2Q 2019 annual review: added maximum dose restriction for concomitant strong CYP2C8 inhibitor use; no significant changes; references reviewed and updated. | 03.05.19 | 05.19 |
| 1Q 2020 annual review: criteria added for new FDA indication: metastatic CSPC; modified to require that a GnRH analog should always be prescribed concurrently with Xtandi unless member has had a bilateral orchiectomy (regardless of metastatic or non-metastatic disease) per FDA labeling and NCCN guidelines; references reviewed and updated. | 01.14.20 | 02.20 |
| RT4: Added new dosage form of 40 and 80 mg tablets | 08.25.20 | |
| 1Q 2021 annual review: oral oncology generic redirection language added; references to HIM.PHAR.21 revised to HIM.PA.154; references reviewed and updated. | 11.10.20 | 02.21 |
| 1Q 2022 annual review: per November SDC and prior clinical guidance, removed HIM line of business (separated to new policy HIM.PA.164); added redirection to generic abiraterone for members with metastatic disease; references reviewed and updated. | 11.30.21 | 02.22 |
| Template changes applied to other diagnoses/indications. | 09.30.22 | |
| 1Q 2023 annual review: added Commercial and HIM lines of business (CP.CPA.203 and HIM.PA.164 retired); removed redirection to abiraterone; references reviewed and updated. | 11.03.22 | 02.23 |

**Important Reminder**

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering

benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

**Note:**
**For Medicaid members**, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.