Clinical Policy: Enzalutamide (Xtandi)

Reference Number: ERX.SPA.142
Effective Date: 03.01.14
Last Review Date: 02.22
Line of Business: Commercial, 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.

Health plan approved formularies should be reviewed for all coverage determinations. Requirements to use preferred alternative agents apply only when such requirements align with the health plan approved formulary.

It is the policy of health plans affiliated with Envolve Pharmacy Solutions™ 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:
Commercial – Length of Benefit
Medicaid – 6 months

B. Other diagnoses/indications
1. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

II. Continued Therapy

A. Prostate Cancer (must meet all)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions 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:
Commercial – Length of Benefit
Medicaid – 12 months

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. Currently receiving medication via a health plan affiliated with Envolve Pharmacy Solutions and documentation supports positive response to therapy.
   Approval duration: Duration of request or 6 months (whichever is less); or
2. Refer to ERX.PA.01 if diagnosis is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized).

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 policy – ERX.PA.01 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
Not applicable

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.; May 2021. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/213674s002lbl.pdf. Accessed November 23, 2021.
2. National Comprehensive Cancer Network Drugs and Biologics Compendium. Available at https://www.nccn.org/professionals/drug_compendium/content/. Accessed November 23, 2021.
3. National Comprehensive Cancer Network. Prostate Cancer Version 1.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed November 23, 2021.
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
3Q 2018 annual review: specialist requirement added; off-label use in castration-naïve prostate cancer removed per NCCN guidelines; modified approval duration from 6/12 months to length of benefit; references reviewed and updated.	05.15.18	08.18
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	11.18

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2019 annual review: no significant changes; added maximum dose restriction for concomitant strong CYP2C8 inhibitor use; 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; added Medicaid line of business with 6/12 month approval durations; 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 reviewed and updated.	11.10.20	02.21
1Q 2022 annual review: no significant changes; references reviewed and updated.	11.23.21	02.22

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.

This Clinical Policy is not intended to dictate to providers how to practice medicine, nor does it constitute a contract or guarantee regarding payment or results. 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.