Evolent Clinical Guideline 3024 for Xtandi™ (enzalutamide)

Guideline Number: Evolent_CG_3024	**Applicable Codes**	
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STATEMENT

Purpose

To define and describe the accepted indications for Xtandi (enzalutamide) usage in the treatment of cancer, including FDA approved indications, and off-label indications.

Evolent is responsible for processing all medication requests from network ordering providers. Medications not authorized by Evolent may be deemed as not approvable and therefore not reimbursable.

The use of this drug must be supported by one of the following: FDA approved product labeling, CMS-approved compendia, National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) clinical guidelines, or peer-reviewed literature that meets the requirements of the CMS Medicare Benefit Policy Manual Chapter 15.

INDICATIONS

Continuation requests for a not-approvable medication shall be exempt from this Evolent policy provided

- The member has not experienced disease progression on the requested medication AND
- The requested medication was used within the last year without a lapse of more than 30 days of having an active authorization AND
- Additional medication(s) are not being added to the continuation request.

Prostate Cancer

- Xtandi (enzalutamide) may be used in combination with an LHRH analog or after orchiectomy (ADT- Androgen Deprivation Therapy) for ANY of the following clinical settings:
    - In members with non-metastatic castration resistant prostate cancer, M0 disease with no visible metastases on conventional imaging, AND a PSA Doubling Time of less than or equal to 10 months OR
    - In members with metastatic castration sensitive/resistant prostate cancer.
- Xtandi (enzalutamide) may be used in members with non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR).
    - nmCSPC is defined as:
        - PSA doubling time ≤ 9 months
        - PSA ≥ 1 ng/mL (post-RP)
        - PSA ≥ 2 ng/mL above the nadir (post-RT)
        - Testosterone level ≥ 150 ng/mL
    - Members receiving Xtandi (enzalutamide) for nmCSPC may be treated with or without a GnRH analog concurrently.

- Xtandi (enzalutamide) may be used with Talzenna (talazoparib) for homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) except for BRCA 1 and 2 mutation positive mCRPC. Xtandi (enzalutamide) may be used with Talzenna (talazoparib) for mCRPC that is positive for any one of the following: ATM, ATR, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCA, FANCL, MLH1, MREL11A, NBN, PALB2, RAD51B, RAD51C, RAD51D, or RAF54L

  The above policy position is based on the lack of Level 1 evidence (randomized trials and/or meta-analyses) to show superior outcomes for patients with BRCA1/2 mutation positive prostate cancer using Talzenna (talazoparib) and Xtandi (enzalutamide) in comparison to the recommended alternatives listed below. The alternative regimens supported by Evolent Policies are: 1) Zejula (niraparib) and Abirtega/Yonsa/Zytiga (abiraterone acetate) with prednisone, 2) Akeega (niraparib and abiraterone acetate) with prednisone, and 3) Lynparza (olaparib) and Abirtega/Yonsa/Zytiga (abiraterone acetate) with prednisone.
- Members receiving Xtandi (enzalutamide) and Talzenna (talazoparib) should also receive a GnRH analog concurrently or should have had bilateral orchiectomy.

CONTRAINDICATIONS/WARNINGS

- None

EXCLUSION CRITERIA

- The member has disease progression while on or after taking Xtandi (enzalutamide), or a similar Androgen Receptor Signaling Inhibitor such as Erleada (apalutamide) OR Nubeqa (darolutamide).
- The member has BRCA 1 and 2 positive mCRPC.
- Xtandi (enzalutamide) is being used concurrently with other anti-cancer therapy including abiraterone, cabazitaxel, docetaxel, sipuleucel-T, apalutamide, or darolutamide.
- Dosing exceeds single dose limit of Xtandi (enzalutamide) of 160 mg.
- Treatment with Xtandi (enzalutamide) exceeds the maximum limit of 120 (40 mg) capsules, 120 (40 mg) tablets, or 60 (80 mg) tablets per month.
- Investigational use of Xtandi (enzalutamide) with an off-label indication that is not sufficient in evidence or is not generally accepted by the medical community. Sufficient evidence that is not supported by CMS recognized compendia or acceptable peer reviewed literature is defined as any of the following:
  - Whether the clinical characteristics of the patient and the cancer are adequately represented in the published evidence.
  - Whether the administered chemotherapy/biologic therapy/immune therapy/targeted therapy/other oncologic therapy regimen is adequately represented in the published evidence.
  - Whether the reported study outcomes represent clinically meaningful outcomes

experienced by patients. Generally, the definitions of Clinically Meaningful outcomes are those recommended by ASCO, e.g., Hazard Ratio of less than 0.80 and the recommended survival benefit for OS and PFS should be at least 3 months.

- Whether the experimental design, considering the drugs and conditions under investigation, is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover).
- That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs.
- That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.
- That abstracts (including meeting abstracts) without the full article from the approved peer-reviewed journals lack supporting clinical evidence for determining accepted uses of drugs.

CODING AND STANDARDS

Codes

- J8999 – enzalutamide

Applicable Lines of Business

☐	CHIP (Children's Health Insurance Program)
☒	Commercial
☒	Exchange/Marketplace
☒	Medicaid
☐	Medicare Advantage

POLICY HISTORY

Date	Summary
February 2026	• Updated references
February 2025	• Converted to new Evolent guideline template • This guideline replaces UM ONC_1228 Xtandi (enzalutamide)
February 2024	• Updated clinical settings verbiage when enzalutamide is used in combination with an LHRH analog or after orchiectomy (ADT- Androgen Deprivation Therapy)

LEGAL AND COMPLIANCE

Guideline Approval

Committee

Reviewed / Approved by Evolent Specialty Services Clinical Guideline Review Committee

Disclaimer

Evolent Clinical Guidelines do not constitute medical advice. Treating health care professionals are solely responsible for diagnosis, treatment, and medical advice. Evolent uses Clinical Guidelines in accordance with its contractual obligations to provide utilization management. Coverage for services varies for individual members according to the terms of their health care coverage or government program. Individual members' health care coverage may not utilize some Evolent Clinical Guidelines. Evolent clinical guidelines contain guidance that requires prior authorization and service limitations. A list of procedure codes, services or drugs may not be all inclusive and does not imply that a service or drug is a covered or non-covered service or drug. Evolent reserves the right to review and update this Clinical Guideline in its sole discretion. Notice of any changes shall be provided as required by applicable provider agreements and laws or regulations. Members should contact their Plan customer service representative for specific coverage information.

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